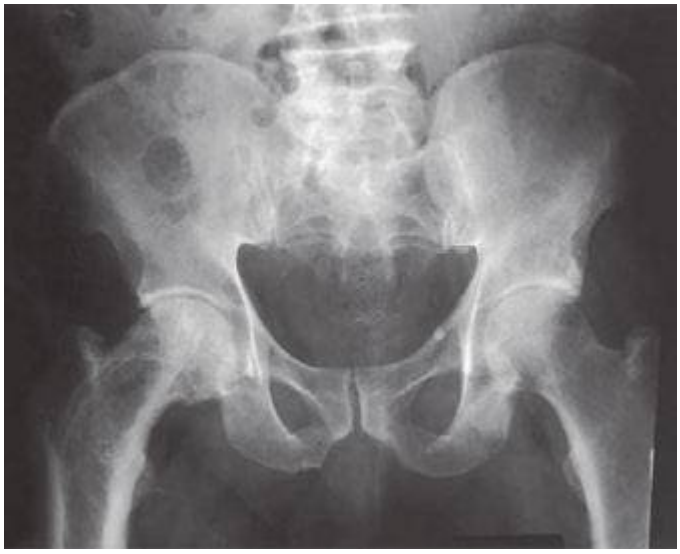

**FIGURE 426e-3 Radiograph of a 73-year-old man with Paget's disease of the right proximal femur.** Note the coarsening of the trabecular pattern with marked cortical thickening and narrowing of the joint space consistent with osteoarthritis secondary to pagetic deformity of the right femur.

CT may be useful for the assessment of possible fracture, and MRI is necessary to assess the possibility of sarcoma, giant cell tumor, or metastatic disease in pagetic bone. Definitive diagnosis of malignancy often requires bone biopsy.

Biochemical evaluation is useful in the diagnosis and management of Paget's disease. The marked increase in bone turnover can be monitored using biochemical markers of bone formation and resorption. The parallel rise in markers of bone formation and resorption confirms the coupling of bone formation and resorption in Paget's disease. The degree of bone marker elevation reflects the extent and severity of the disease. Patients with the highest elevation of ALP (10 × the upper limit of normal) typically have involvement of the skull and at least one other skeletal site. Lower values suggest less extensive involvement or a quiescent phase of the disease. For most patients, serum total ALP remains the test of choice both for diagnosis and assessing response to therapy. Occasionally, a symptomatic patient with evidence of progression at a single site may have a normal total ALP level but increased bone-specific ALP. For unclear reasons, serum osteocalcin, another marker of bone formation, is not always elevated and is not recommended for use in diagnosis or management of Paget's disease. Bone resorption markers (serum or urine N-telopeptide or C-telopeptide measured in the blood or urine) are also elevated in active Paget's disease and decrease more rapidly in response to therapy than does ALP.

Serum calcium and phosphate levels are normal in Paget's disease. Immobilization of a patient with active Paget's disease may rarely cause hypercalcemia and hypercalciuria and increase the risk for nephrolithiasis. However, the discovery of hypercalcemia, even in the presence of immobilization, should prompt a search for another cause of hypercalcemia. In contrast, hypocalcemia or mild secondary hyperparathyroidism may develop in Paget's patients with very active bone formation and insufficient calcium and vitamin D intake, particularly during bisphosphonate therapy when bone resorption is rapidly suppressed and active bone formation continues. Therefore, adequate calcium and vitamin D intake should be instituted prior to administration of bisphosphonates.

## TREATMENT PAGET'S DISEASE OF BONE

The development of effective and potent pharmacologic agents **(Table 426e-1)** has changed the treatment philosophy from treating only symptomatic patients to treating asymptomatic patients who are at risk for complications. Pharmacologic therapy is indicated in the following circumstances: to control symptoms caused by metabolically active Paget's disease such as bone pain, fracture, headache, pain from pagetic radiculopathy or arthropathy, or neurologic complications; to decrease local blood flow and minimize operative blood loss in patients who need surgery at an active pagetic site; to reduce hypercalciuria that may occur during immobilization; and to decrease the risk of complications when disease activity is high (elevated ALP) and when the site of involvement involves weight-bearing bones, areas adjacent to major joints, vertebral bodies, and the skull. Whether or not early therapy prevents late complications remains to be determined. A randomized study of over 1200 patients from the United Kingdom showed no difference in bone pain, fracture rates, quality of life, and hearing loss between patients who received pharmacologic therapy to control symptoms (bone pain) and those receiving bisphosphonates to normalize serum ALP. However, the most potent agent (zoledronic acid) was not used, and the duration of observation (mean of 3 years with a range of 2 to 5 years) may not be long enough to assess the impact of treatment on long-term outcomes. It seems likely that the restoration of normal bone architecture following suppression of pagetic activity will prevent further deformities and complications.

**TABLE 426e-1 PHARMACOLOGIC AGENTS APPROVED FOR TREATMENT OF PAGET'S DISEASE**

| Name | Dose and Mode of Delivery | Normalization of ALP |
|---|---|---|
| Zoledronic acid | 5 mg IV over 15 min | 90% of patients at 6 mo |
| Pamidronate | 30 mg IV/d over 4 h on 3 days | ~50% of patients |
| Risedronate | 30 mg PO/d for 2 mo | 73% of patients |
| Alendronate | 40 mg PO/d for 6 mo | 63% of patients |
| Tiludronate | 800 mg PO daily for 3 mo | 35% of patients |
| Etidronate | 200–400 mg PO/d × 6 mo | 15% of patients |
| Calcitonin (Miacalcin) | 100 U SC daily for 6–18 mo (may reduce to 50 U 3 × per wk) | (Reduction of ALP by up to 50%) |

Agents approved for treatment of Paget's disease suppress the very high rates of bone resorption and secondarily decrease the high rates of bone formation (Table 426e-1). As a result of decreasing bone turnover, pagetic structural patterns, including areas of poorly mineralized woven bone, are replaced by more normal cancellous or lamellar bone. Reduced bone turnover can be documented by a decline in serum ALP and urine or serum resorption markers (N-telopeptide, C-telopeptide).

The first clinically useful agent, etidronate, is now rarely used because the doses required to suppress bone resorption may impair mineralization, necessitating that the drug be given for a maximum of 6 months followed by a 6-month drug-free period. The second-generation oral bisphosphonates—tiludronate, alendronate, and risedronate—are more potent than etidronate in controlling bone turnover and, thus, induce a longer remission at a lower dose. The lower doses reduce the risks of impaired mineralization and osteomalacia. Oral bisphosphonates should be taken first thing in the morning on an empty stomach, followed by maintenance of upright posture with no food, drink, or other medications for 30–60 min. The efficacy of different agents, based on their ability to normalize or decrease ALP levels, is summarized in Table 426e-1, although the response rates are not comparable because they are obtained from different studies.

Intravenous bisphosphonates approved for Paget's disease include pamidronate and zoledronic acid. Although the recommended dose for pamidronate is 30 mg dissolved in 500 mL of normal saline or dextrose IV over 4 h on 3 consecutive days, a more commonly used simpler regimen is a single infusion of 60–90 mg in patients with mild elevation of serum ALP and multiple 90-mg