Paget's Disease of Bone

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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 73-year-old man presents with a 5-year history of low back pain that is exacerbated by standing. During the past year, pain has developed in his buttocks and legs when he walks, and it is not relieved by acetaminophen. The neurologic examination is unremarkable. Radiographs of the spine show coarsening of the trabecular pattern in several lumbar and lower thoracic vertebrae and expansion of several lumbar vertebral bodies. The total serum alkaline phosphatase level is 350 U per liter (reference range, 40 to 125); the results of liver-function tests and other routine laboratory tests are normal. How should he be further evaluated and treated?

THE CLINICAL PROBLEM

Paget's disease of bone is a common disorder characterized by focal areas of increased and disorganized bone remodeling affecting one or more bones throughout the skeleton. It preferentially targets the axial skeleton, most frequently affecting the pelvis (70% of cases), femur (55%), lumbar spine (53%), skull (42%), and tibia (32%). Paget's disease is rare before the age of 55 years, but increases in prevalence thereafter, in some countries affecting about 5% of women and 8% of men by the eighth decade of life. The disease predominantly affects people of European descent and is rare in Africans, people from the Indian subcontinent, and Asians. These differences in susceptibility probably have a genetic basis and are consistent with the hypothesis that the disease originated in northwestern Europe through one or more founder mutations and spread elsewhere through emigration. Infection has been proposed as a potential trigger on the basis of the observation of intranuclear inclusion bodies resembling paramyxovirus nucleocapsids in pagetic osteoclasts. The identity of these structures is uncertain, however, and they may represent abnormal protein aggregates resulting from defects of the autophagy pathway. There is experimental evidence that infection of osteoclast precursors with paramyxoviruses and overexpression of viral proteins increase osteoclast activity, but data on the persistence of infection in patents are conflicting. The incidence and severity of Paget's disease of bone have decreased in recent years, possibly reflecting changes in environmental factors that may mitigate the predisposition to disease, such as improved nutrition, reduced exposure to infections, and a more sedentary lifestyle, which has had the effect of reducing mechanical loading of the skeleton and the number of skeletal injuries.

Several rare inherited forms of Paget's disease of bone are recognized; they are caused by mutations in genes that affect osteoclast differentiation and function (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). About 35% of patients with classic Paget's disease have a positive family history, and in these families the disease is inherited in an autoso-
Although Paget's disease of bone may be an incidental finding on radiographic examination or biochemical testing, up to 40% of patients who come to medical attention present with bone pain.

Patients with Paget's disease of bone should be carefully evaluated to determine whether their pain results from increased metabolic activity, a complication such as osteoarthritis, or a coexisting musculoskeletal condition.

Bisphosphonates are the treatment of first choice and are indicated in patients with pain localized to an affected site in which the cause is thought to be increased metabolic activity.

Analgesics, nonsteroidal anti-inflammatory drugs, and antineuropathic drugs may control pain that does not respond to bisphosphonates.

Bisphosphonates can normalize bone turnover in a high proportion of patients, but evidence that long-term suppression of bone turnover improves the clinical outcome or prevents complications is currently lacking.

Paget's disease of bone is often an elevated serum alkaline phosphatase level or an abnormal radiograph in a patient whose health is being investigated for other reasons. Between 30 and 40% of patients have symptoms at the time of diagnosis, although the overall proportion of patients with symptoms is believed to be substantially lower (5 to 10%), since many cases never come to medical attention. The most common symptom is bone pain, which may be due to increased bone turnover or a complication such as osteoarthritis, spinal stenosis, or pseudofracture. Deafness may occur in patients with skull involvement. Osteosarcoma is a rare complication (present in less than 0.5% of cases) but should be suspected in patients who have a sudden increase in bone pain or swelling. Other rare complications include obstructive hydrocephalus, high-output cardiac failure, and hypercalcemia in patients who are immobilized. Clinical signs include bone deformity (Fig. 1) and warmth of the skin overlying an affected bone. Many patients have no appreciable signs of Paget's disease on examination.

The diagnosis can usually be made on the basis of a radiograph showing the typical features of focal osteolysis with coarsening of the trabecular pattern, bone expansion, and cortical thickening (Fig. 1). The extent of disease is best determined on radionuclide bone scans, which can be helpful if new symptoms develop at sites distant from those identified on radiographs. The use of magnetic resonance imaging or computed tomography is not routinely indicated, although it does have a role in selected patients in whom complications such as spinal stenosis or osteosarcoma are suspected. Laboratory testing should include assessment of renal function and measurement of levels of calcium, albumin, alkaline phosphatase, and 25-hydroxyvitamin D3; liver function should be assessed to rule out the possibility that elevations in the alkaline phosphatase level are of hepatic origin. Typically, patients with Paget's disease of bone present with an isolated elevation in the alkaline phosphatase level, with otherwise normal results of biochemical testing. However, normal levels of alkaline phosphatase do not rule out the diagnosis. Vitamin D deficiency is a common finding, probably reflecting the fact that Paget's disease of bone predominantly affects older people, among whom vitamin D deficiency is prevalent. Tests for specialized markers,
such as bone-specific alkaline phosphatase or procollagen type I N-terminal propeptide, can be useful in patients with coexisting liver disease but otherwise offer little advantage over measurement of the total serum alkaline phosphatase level for the purpose of diagnosis and assessment of treatment response. The differential diagnosis includes hyperostosis frontalis interna (a benign condition characterized by sclerosis of the frontal bones of the skull), fibrous dysplasia, pustulotic arthropathy (which can be manifested as sclerotic lesions of the clavicle and ribs), and osteosclerotic metastases. However, Paget's disease of bone is seldom confused with these other disorders, and biopsy of an affected site is rarely required for diagnosis.

TREATMENT

The principal indication for antiresorptive therapy is bone pain thought to be caused by increased metabolic activity. There is no evidence that asymptomatic patients benefit from antiresorptive therapy. Patients with Paget's disease who present with pain should be carefully evaluated for causes other than increased metabolic activity, such as nerve-compression syndromes, pseudofractures, secondary osteoarthritis, or another musculoskeletal condition. The most straightforward case is an elevated alkaline phosphatase level with bone pain localized to an affected site. In such cases, the pain can confidently be attributed to increased metabolic activity and typically responds well to antiresorptive therapy. The source of pain in patients with Paget's disease of the spine or pelvis is often less clear. Pagetic pain can be present at rest and at night but often becomes worse on weight bearing, which makes differentiation from osteoarthritis difficult.

In such cases, it is reasonable to begin a therapeutic trial of bisphosphonates in order to determine whether increased metabolic activity is a contributing factor. If there is not adequate abatement of the pain, further evaluation is warranted to identify the cause and provide appropriate treatment.

Pseudofractures (narrow radiolucency bands that traverse the cortex of long bones) represent a distinct problem in disease management. They can develop in the lateral cortex of weight-bearing bones in the lower limbs, such as the femur, and they may be asymptomatic or associated with bone pain localized to the affected site. Some pseudofractures regress spontaneously or remain stable for prolonged periods, and some progress to pathologic fracture. Clinical experience suggests that pseudofractures do not respond to calcitonin therapy and that treatment with etidronate may increase the risk of progression to pathologic fracture. The effect of aminobisphosphonates on pseudofractures is unknown. Asymptomatic pseudofractures can be treated conservatively, but increasing pain at an affected site is generally considered an indication for surgical stabilization.

Bisphosphonates

The drugs of first choice in the treatment of Paget's disease of bone are nitrogen-containing bisphosphonates (aminobisphosphonates) such as alendronate, pamidronate, risedronate, and zoledronic acid, which preferentially target affected sites and are highly effective at suppressed...
Table 1. Bisphosphonates Used in the Treatment of Paget's Disease of Bone.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etidronate†</td>
<td>400 mg/day for 3-6 mo</td>
<td>Diarrhea, nausea, abdominal pain</td>
</tr>
<tr>
<td>Tiludronate†</td>
<td>400 mg/day for 3 mo</td>
<td>Diarrhea, nausea, dyspepsia</td>
</tr>
<tr>
<td>Risedronate†</td>
<td>30 mg/day for 2 mo</td>
<td>Dyspepsia, esophagitis</td>
</tr>
<tr>
<td>Alendronate†§</td>
<td>40 mg/day for 6 mo</td>
<td>Dyspepsia, esophagitis</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate†</td>
<td>30-60 mg/day for 3 days</td>
<td>Acute-phase response, hypocalcemia</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>5 mg, single infusion</td>
<td>Acute-phase response, hypocalcemia</td>
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* Etidronate is now seldom used.
† This drug should be avoided in patients with an estimated glomerular filtration rate (GFR) of less than 30 ml per minute per 1.73 m² of body-surface area.
‡ Alendronate is not licensed for the treatment of Paget's disease of bone in the United Kingdom or other European countries.
§ This drug should be avoided in patients with an estimated GFR of less than 35 ml per minute per 1.73 m² of body-surface area.

...ing the increased bone turnover that is characteristic of active Paget's disease.25-28 Table 1 summarizes the bisphosphonates currently used in treatment. Randomized trials have shown aminobisphosphonates to be superior to simple bisphosphonates such as etidronate and tiludronate in suppressing bone turnover in Paget's disease, but not in improving symptoms.29,30 Levels of alkaline phosphatase start to fall within about 10 days after the commencement of bisphosphonate treatment and reach a nadir between 3 and 6 months. Symptoms can improve while alkaline phosphatase levels are elevated but still falling, and good clinical responses are often observed in patients whose alkaline phosphatase levels are not restored to normal.

There are limited data available on the direct comparisons of different aminobisphosphonates in the treatment of Paget's disease. In a 2-year open-label study comparing intravenous administration of 60 mg of pamidronate every 3 months with daily oral administration of 40 mg of alendronate in 3-month blocks, there were no significant differences in the proportion of patients whose alkaline phosphatase levels became normal (88% and 91%, respectively) or the proportion of patients who had an improvement in symptoms.30 In a randomized, double-blind trial comparing a single intravenous infusion of 5 mg of zoledronic acid with oral administration of 30 mg of risedronate daily for 2 months, normalization of alkaline phosphatase levels was achieved at 6 months in 89% and 58% of patients, respectively. Those receiving zoledronic acid had greater improvement in some domains of health-related quality of life, but the changes observed were small — 1 to 2 points, which is below the threshold of 5 points for a change that is considered to be clinically significant.31

Intravenous bisphosphonates often cause transient bone pain, myalgia, headache, nausea, pyrexia, and fatigue within 1 to 3 days after the infusion (acute-phase response).31,32 These symptoms can be ameliorated if acetaminophen is administered before and for a few days after the infusion, but they almost always subside within 7 days, even without treatment. The acute-phase response is much less common after second and subsequent infusions.32 Hypocalcemia may also occur, particularly in patients with substantial elevations in bone turnover and vitamin D deficiency. The risk can be minimized by correcting vitamin D deficiency before treatment and providing calcium and vitamin D supplements for the first 1 or 2 weeks after the infusion.

Patients taking oral bisphosphonates must fast for 30 minutes (in the case of risedronate and alendronate) or 120 minutes (in the case of etidronate and tiludronate) before and after dosing to achieve adequate absorption. For this reason, it is customary to advise patients to take the medications first thing in the morning. The most common adverse effects are dyspepsia (with risedronate and alendronate) and diarrhea (with...
with the intent of reducing operative blood loss, as suggested before orthopedic and spinal surgery, and spinal stenosis. Osteotomy can also be used to attempt to correct deformity in weight-bearing limbs. Surgical treatment of Paget's disease can be technically challenging because of deformity, osteosclerosis, and increased vascularity, but evidence from case series indicates that fractures of pagetic bone heal normally and that joint-replacement surgery has a good outcome. Administration of a bisphosphonate has been suggested before orthopedic and spinal surgery, with the intent of reducing operative blood loss, but the effectiveness of this approach has not been studied. There is a theoretical concern that previous bisphosphonate therapy might impair fracture union and bone repair, but there is little evidence to suggest that this is a problem in clinical practice. Orthopedic surgery may also be required in patients with osteosarcoma, but the prognosis in such cases is poor, even with aggressive operative treatment.

Nonpharmacologic treatment and the response to treatment are typically assessed by measuring alkaline phosphatase levels, although levels can be normal in patients with localized disease that is metabolically active. Further courses of treatment should be considered in patients with recurrent or persistent pain in whom alkaline phosphatase levels remain or become elevated.

**Areas of Uncertainty**

Bisphosphonates promote the healing of osteolytic lesions and improve bone histologically. For this reason, some clinicians believe that bisphosphonates should be administered as prophylaxis against complications in young patients; those with disease of the skull, spine, or long bones; and those with disease that is close to a major joint. However, there are insufficient data to determine whether this approach improves the long-term outcome. There are also insufficient data to determine whether maintaining alkaline phosphatase levels within the normal range reduces the risk of complications. In an observational study of patients treated with etidronate, there was no significant difference in complication rates after 5 years between patients with normal alkaline phosphatase levels and patients with levels that remained elevated, but the proportion of patients whose levels of alkaline phosphatase had normalized was small, and the study had limited power. In another study, patients were randomly assigned to receive symptomatic treatment, intended to control bone pain, or intensive treatment, intended to normalize alkaline phosphatase levels. Alkaline phosphatase levels were maintained within the normal range for a period of 2 to 4 years in 50% of patients in the group receiving symptomatic treatment and in 80% of patients in the group receiving intensive treatment, but there were no significant between-group differences in the rate of fractures or orthopedic procedures or in the quality of life. A follow-up study of the
subset of patients whose alkaline phosphatase levels had been normalized during the trial compared the use of a single infusion of zoledronic acid with a 2-month course of oral risedronate. Better quality-of-life scores and more prolonged suppression of alkaline phosphatase levels were reported for the patients receiving zoledronic acid, but complications were not assessed.

GUIDELINES FROM PROFESSIONAL SOCIETIES

The Bone Research Society of the United Kingdom has published guidelines for the management of Paget’s disease.47 The guidelines underscore the point that the only indication for antiresorptive therapy in Paget’s disease for which there is firm evidence of a clinical benefit is bone pain thought to be caused by increased metabolic activity (level of evidence I). The guidelines also note that aminobisphosphonates are superior to simple bisphosphonates in suppressing alkaline phosphatase levels but that there is no significant difference between these bisphosphonates in their effects on bone pain. The recommendations in this review are concordant with these guidelines but also take into account the study by Reid et al.,48 which postulates the publication of the guidelines, suggesting that there may be a slightly greater symptomatic response with zoledronic acid than with risedronate.

REFERENCES

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CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has radiographic findings that are typical of Paget’s disease of bone and an elevated alkaline phosphatase level, which suggests increased metabolic activity, but the patient also has symptoms suggestive of spinal stenosis. Bisphosphonate therapy is indicated in patients with Paget’s disease when there is localized pain in an affected bone that is attributable to increased metabolic activity; asymptomatic disease does not require treatment. In this patient, it is uncertain whether Paget’s disease is causing the pain. A trial of an oral bisphosphonate such as risedronate or an intravenous bisphosphonate such as zoledronic acid would be reasonable (after checking levels of 25-hydroxyvitamin D and providing for repletion if levels are low); the absence of a response after 3 to 4 months would suggest an alternative cause of pain, which would require further evaluation and other treatment.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.


