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# Paget disease of bone: Diagnosis and drug therapy

## ABSTRACT

Paget disease of bone is a focal disorder of aging bone that may be asymptomatic or may present with pain, bowing deformity, fracture, or a nonspecific rheumatic complaint. It is the second most common disease of bone in the elderly after osteoporosis, and the loss of structural integrity in affected bone conveys a risk of fracture. It may occur sporadically or in geographic or familial clusters. This article discusses the prevalence, pathology, workup, and treatment of Paget disease of bone.

## KEY POINTS

The variable prevalence of Paget disease in different geographic regions and its sometimes-familial expression suggest a genetic predisposition or an environmental factor, or both.

Because Paget disease tends to occur in an aging skeleton, "pagetic" bone may not always be the source of pain. Rather, the pain may be from secondary degenerative changes of the spine or joints or from compression fractures.

An elevated serum alkaline phosphatase level may signal Paget disease, but many patients have a normal serum alkaline phosphatase.

Plain radiography of the affected bones outlines the anatomy of the problem and provides insight into the cause of pain.

Treatment of Paget disease relies primarily on the new generation of nitrogen-containing bisphosphonates.

**P**AGET DISEASE OF BONE is a focal disorder of the aging skeleton that can be asymptomatic or can present with pain, bowing deformities, fractures, or nonspecific rheumatic complaints. Physicians often discover it in asymptomatic patients when serum alkaline phosphatase levels are elevated or as an incidental finding on radiography. Despite evidence of germline mutations and polymorphisms that predispose to Paget disease, the environmental determinants that permit disease expression in older people remain unknown.

## A STRIKING GEOGRAPHIC DISTRIBUTION

Researchers have been studying the determinants and distribution of Paget disease ever since Sir James Paget first described it in 1877.<sup>1</sup>

Paget disease has a predilection for the axial skeleton, particularly the lumbosacral spine and pelvis, as well as the skull, femur, and tibia.<sup>2</sup> Knowing this, investigators have used screening plain films of the abdomen (kidney-ureter-bladder views) to estimate its prevalence in different populations, as these images capture the lumbosacral spine, pelvis, and proximal femurs. Other means of assessing prevalence have included autopsy series, questionnaires, and screens for biochemical markers of bone turnover, such as elevated serum alkaline phosphatase from bone.<sup>3-6</sup>

Using these methods, Paget disease has been estimated to occur in 1% to 3% of people over age 55, and in as many as 8% of people over age 80 in certain countries.<sup>7</sup>

This disease has a striking geographic distribution, being frequent in Europe, Canada, the United States, Australia, New Zealand, and cities of South America, but rare in Scan-

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dinavia and Japan. It seems to be equally rare in other countries of the Far East and in India, Russia, and Africa, although its prevalence in these areas has not been thoroughly investigated.<sup>8</sup>

That it is an ancient disease has been corroborated by excavations in churchyards in Great Britain.<sup>9,10</sup> It may be familial or sporadic, but its expression is delayed until late middle age in most persons, and it does not occur in children. For reasons unclear, the prevalence seems to be decreasing in many countries.<sup>11–13</sup>

## ■ GENETICS IS NOT THE WHOLE STORY

The variable prevalence of Paget disease in different geographic regions and its sometimes-familial expression suggest a genetic predisposition, environmental factor, or both.

### Mutations in *SQSTM1*

In 2002, scientists investigating a cohort of French Canadian families found a mutation in the *SQSTM1* gene that was present in almost 50% of people with familial Paget disease and in 16% of those with sporadic Paget disease.<sup>14</sup> Hocking and his colleagues in the United Kingdom subsequently found the same mutation in 19% of cases of familial Paget disease and in 9% of sporadic cases.<sup>15</sup>

Further, investigators noted that the mutation was often present on a conserved haplotype, consistent with a stable genetic change occurring in the affected population.<sup>16</sup> This observation of a “founder effect” dovetailed with the epidemiology of Paget disease,<sup>17</sup> but only with this *SQSTM1* mutation.

Throughout Europe, Australia, and the United States, comparable rates of the *SQSTM1* mutation were reported in or around the ubiquitin-associated domain. Several specific mutations exist, the most common one being P392L, ie, a proline-to-leucine substitution at amino acid 392. Scientists have tried to correlate severity of disease with genotype, but the findings have been inconsistent.<sup>18–21</sup>

Investigations into the mechanism of disease have pointed to the role of p62, the product of *SQSTM1*, in signaling osteoclast activation via nuclear factor kappa B. Since this initial discovery, polymorphisms in the genes affecting osteoclast maturation, activa-

## Glossary of drugs discussed in this article

Alendronate (Fosamax)

Calcitonin (Fortical, Miacalcin)

Denosumab (Prolia, Xgeva)

Etidronate (Didronel)

Pamidronate (Aredia)

Risedronate (Actonel, Atelvia)

Tiludronate (Skelid)

Zoledronic acid (Reclast)

tion, and fusion pathways have been shown to predispose to Paget disease. Examples:

- *TNFRSF11A*, which codes for receptor activator of nuclear factor kappa B, or RANK
- *TNFRSF11B*, which codes for osteoprotegerin, or OPG
- *CSF1*, which codes for macrophage colony-stimulating factor 1, and
- *OPTN*, which codes for optineurin, a member of the nuclear factor kappa B-modulating protein family.

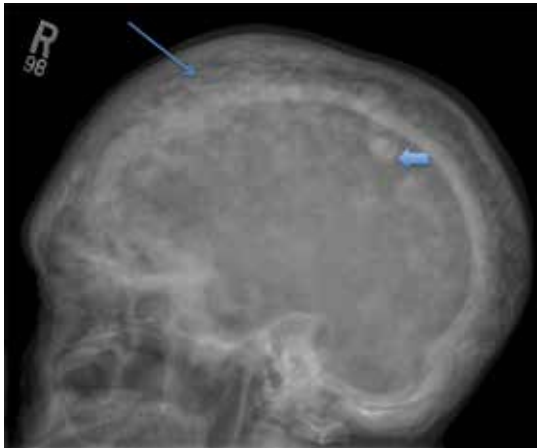
Clinicians interested in these details can read an excellent review of the pathogenesis of Paget disease.<sup>22</sup>

### Other possible factors

Although there is good evidence that measles and canine distemper virus can infect osteoclasts and modify their phenotype, there is no good evidence that these infections by themselves cause Paget disease.<sup>23–25</sup> It is, however, tempting to think of these RNA paramyxoviruses as precipitating factors; conceivably, an infectious agent might seed the ends of long bones, accounting for the fixed distribution of Paget disease and its late expression.

Epidemiologic studies from around the world have failed to identify conclusively any environmental exposure that predisposes to Paget disease, although a rural setting, trauma, infection, and milk ingestion have all been proposed.<sup>26–28</sup> It is also possible that as bone ages and the marrow becomes less cellular and more fatty, these changes may permit the disease to develop.

**For reasons unclear, the prevalence of Paget disease seems to be decreasing in many countries**



**FIGURE 1.** Lateral view of the skull of an elderly person who suffers from headache and hearing loss due to Paget disease. Note the thickened skull (thin arrow), and the “cotton wool” spots (thick arrow) that characterize the osteoblastic response.

The greatest risk factor for Paget disease is perhaps aging, followed by ancestry and a known family history of it. That genetics is not the whole story is evident by reports of people with *SQSTM1* mutations who show no clinical evidence of Paget disease in their old age, and patients with Paget disease who have no *SQSTM1* mutation.<sup>20,29</sup>

## CLINICAL PRESENTATION

Most patients with Paget disease have no symptoms and come to medical attention because of an elevated serum alkaline phosphatase level or characteristic findings on radiographs ordered for other indications.<sup>11</sup> Paget disease is the second most common disorder of aging bone after osteoporosis. Yet unlike osteoporosis, which presents as a systemic fragility of bone, the clinical manifestations of Paget disease depend on which bones are affected and how enlarged or misshapen they have become.

### Common complications

As a consequence of this abnormal bone remodeling and overgrowth, many patients present with bone pain. Bone deformity, headache, and hearing loss may also occur (FIGURE 1), as well as fractures and nerve compression syndromes (eg, spinal stenosis, sciatica, cauda equina syndrome).



**FIGURE 2.** Long-standing Paget disease of the right hemipelvis, with thickening of the iliopectineal line (blue arrow) characteristic of Paget disease, and distortion and overgrowth of the right pelvis. Note that the disease does not cross joint lines, sparing the sacrum and left hemipelvis. This woman has monostotic Paget disease. She presented 20 years ago with an elevated serum alkaline phosphatase (765 U/L). She has not had pain, although degenerative changes are evident in the right hip, and physical examination showed some loss of range of motion. Treated for both breast and renal cancer during this time, she has never had any known metastases to bone (see text).

It is important to remember that “pagetic” bone may not be the source of pain, and that functional impairment caused by degenerative changes at affected sites is common (FIGURE 2).<sup>30,31</sup>

In a study from the New England Registry for Paget’s Disease,<sup>32</sup> most patients knew fairly well which bones were affected and what complications resulted from this when deformity, fracture, or total joint replacement had occurred.<sup>32</sup> Although Paget disease did affect their quality of life as measured by physical functioning on the Short Form-12 assessment, these impairments did not seem to affect their outlook, which was as good as or better than that in other people their age.

Pain in  
Paget disease  
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## Metabolic complications

Metabolic complications of Paget disease are rare today but can occur in an elderly patient who has active, polyostotic (multibone) disease.<sup>33</sup> The accelerated rate of bone remodeling and the increased vascularity of pagetic bone have been reported to lead to high-output heart failure. In theory, treatment should ease this by diminishing blood flow to pagetic bone and restoring bone turnover to more normal levels.<sup>34</sup>

**Hypercalcemia** can occur when patients with Paget disease are immobilized for any reason, and there is probably a higher incidence of renal stones in patients with Paget disease.<sup>35,36</sup>

## Malignant complications

**Osteosarcoma** rarely arises in pagetic bone. Yet Paget disease may account for a significant number of cases of this cancer in the elderly.<sup>37</sup> In these cases, osteosarcoma is presumed to be driven by a second genetic mutation, has a genetic signature distinct from that in osteosarcomas occurring in youth, and is quite resistant to treatment.<sup>38</sup> In Scandinavia and Japan, where Paget disease is rare, the second peak of osteosarcoma that occurs with aging seems muted as well.<sup>39,40</sup> These cancers present with pain, soft-tissue swelling, and variable elevations in serum alkaline phosphatase. Investigations to date suggest that pagetic lesions and osteosarcomas arising in pagetic bone are probably both driven to some extent by stromal cells overexpressing RANK ligand and may not represent defects intrinsic to the osteoclast.<sup>41</sup>

**Giant-cell tumors of bone** are also rare but can arise in pagetic bone. A cluster of cases was reported in Avellino and other towns of southern Italy.<sup>42</sup> Again, the lesions occur in older individuals and in different sites than those seen in the benign giant-cell tumors recorded in patients without Paget disease.

**Metastases** from lymphomas, prostate cancer, and breast cancer certainly occur in bone, but rarely in pagetic sites.<sup>43</sup> A recent case study noted that patients with prostate cancer who also had Paget disease had a later onset of metastasis to bone than patients without coincident Paget disease.<sup>44</sup>

## A THOUGHTFUL ASSESSMENT

Evaluating a patient with Paget disease requires a thoughtful assessment of its musculoskeletal consequences in an aging skeleton. Pain in Paget disease is often multifactorial. In the elderly, end-stage degenerative disease of the spine, hip, and knees, mechanical instability, compression fractures of the spine, and neuropathies may compound the clinical picture. Therefore, a thorough evaluation is required to plan effective therapy.

## Alkaline phosphatase and other markers

A screening serum alkaline phosphatase level is usually sufficient to measure bone turnover. Produced by osteoblasts, alkaline phosphatase is a marker of bone formation, but an imperfect one. Often it is elevated in active Paget disease—but not always.<sup>45</sup> Many patients have normal serum alkaline phosphatase levels, particularly if they have monostotic (single-bone) disease. It is unclear why, in a disorder marked by accelerated bone remodeling, the biochemical markers are inconsistent measures of bone turnover.

Research into biochemical markers of Paget disease has had two aims: to identify the single best marker for baseline assessment of pagetic bone activity and to find out whether this measurement responds to therapy.<sup>46,47</sup> Measures of bone formation such as bone-specific alkaline phosphatase, osteocalcin, and the procollagen type I peptides, and measures of bone resorption including the pyridinolines, hydroxyproline, and cross-linked collagens, have been analyzed as markers of bone remodeling and show no real advantage over the serum alkaline phosphatase level as reflections of bone turnover. As alkaline phosphatase measurement is inexpensive, available, and reliable, it should be used preferentially, with gamma-glutamyl transpeptidase or 5' nucleotidase confirming the source as either liver or bone. Readers are directed to a recent review in which the utility of these markers is explored in more detail.<sup>48</sup>

**Alkaline phosphatase is often elevated in active Paget disease, but not always**

## Imaging studies

**Bone scans** can give us an idea of the extent, location, and general activity of the disease (**FIGURE 3**). Uptake is avid in affected



**A.** A typical bone scan showing polyostotic Paget disease, here affecting the right femur, left proximal shoulder, and right hemipelvis. Paget disease does not cross joints into adjacent bone, nor, once defined by bone scan, does it seem to metastasize to new sites.



**B.** The left humeral head. Plain films demonstrate the misshapen bone and classic findings of Paget disease with enlargement of the bone, coarsened trabeculae, and mixed lytic-sclerotic lesions extending distally through the humerus.



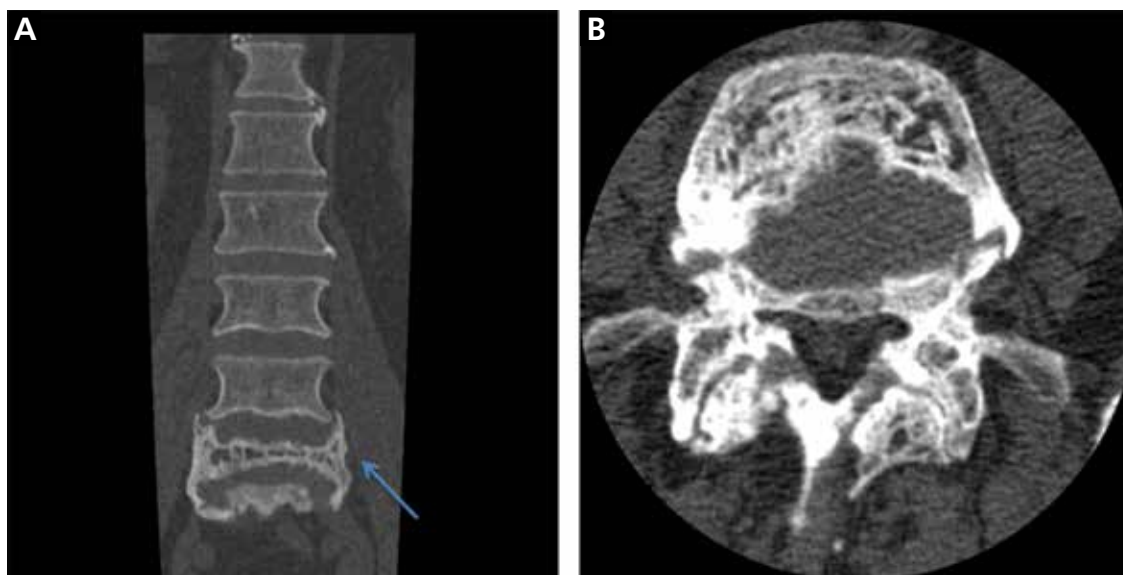
**C.** The femur is sclerotic, and the lateral cortex is bowed. An advancing lytic lesion is seen distally (arrow).



**D.** A "chalk-stick" fracture through the pagetic limb (arrow) of the same patient. The fracture extends through the bone, which breaks like a piece of chalk. Note that in healing, pagetic bone extends through the new callus.

**FIGURE 3**





**FIGURE 4.** (A) Compression fracture of the lumbar spine through a pagetic vertebral body (arrow) in a middle-aged man presenting with pain and clinical symptoms of spinal stenosis. (B) With computed tomography, a reconstructed view of the fourth lumbar vertebral body shows disorganized trabeculae, with Paget disease extending into the posterior processes.

bones, beginning in the subchondral region and spreading throughout the bone. Bone scans can be particularly useful in defining sites of active disease when the serum alkaline phosphatase level is normal.

**Plain radiography** of the affected bones outlines the anatomy of the problem and gives some insight into the cause of pain (FIGURE 3).

**Computed tomography or magnetic resonance imaging** may prove useful in cases of spinal stenosis, cauda equina syndrome, compression fractures, or suspected malignancy (FIGURE 4), but these studies are expensive and generally are not needed.

**Radiographic features.** Paget disease is presumed to be a disease of the osteoclast, and the earliest lesion is described as lytic. In my own experience, it is unusual to see a purely lytic lesion, although sometimes the disease presents in the skull in this way—osteoporosis circumscripta—or in the femur or tibia with an advancing edge of pure osteolysis.

More often, one sees evidence of both resorption by osteoclasts and formation by osteoblasts, reflecting the coupling of these two processes in this disease. Radiographic findings on plain films are usually definitive, showing enlargement of the affected bone, de-

formity, coarsened trabeculae, and thickened cortices with tunneling (FIGURE 5).<sup>49</sup> In weight-bearing bones, pseudofractures may stud the convex surface. These incongruities of bone may persist for years, heralding fracture only when there is focal pain (FIGURE 6).<sup>50</sup>

### Biopsy is infrequently needed

If these diagnostic findings are not present, then biopsy is indicated. In the United States and Canada, where Paget disease is fairly common, biopsy is infrequently needed and is usually reserved for situations in which the differential diagnosis includes cancer, as when the cortex cannot be clearly visualized, the lesions are atypical in pattern or location, or there is a single sclerotic vertebral body on imaging.<sup>51</sup>

The other indication for biopsy is a “new” pagetic lesion. For reasons unknown, the pattern of skeletal involvement in Paget disease tends to be stable throughout the patient’s lifetime. This is another reason why a baseline bone scan is useful.

### ■ TREATMENT WITH BISPHOSPHONATES

Treatment of Paget disease today relies for the most part on the new generation of nitrogen-containing bisphosphonates. As a class, these

**Biopsy is indicated only when radiographic images are not diagnostic**



**FIGURE 5.** Classic changes of Paget disease, beginning in the proximal tibia, with thickened bone, cortical tunneling (thick arrow) and mixed sclerotic-lytic lesions. An advancing leading edge of bone resorption is present (thin arrow).

Though rare, osteosarcoma may arise in pagetic bone

are antiresorptive agents that inhibit osteoclasts; in this way they slow bone remodeling and enhance the deposition of normal lamellar bone. Their clinical efficacy in Paget disease, coupled with the observation that the earliest lesion in Paget disease is lytic, underscores the principle that Paget disease is a disorder of the osteoclast.

## Oral bisphosphonates

**Etidronate**, approved in 1977, was the first bisphosphonate licensed to treat Paget disease, and it remains available for this indication in the United States. Used in 6-month regimens, it lowers the serum alkaline phosphatase level in some patients, but it has a narrow therapeutic margin. Drug-induced osteomalacia and worsening lytic lesions and fractures in weight-bearing bones are some of the complications.<sup>52</sup> When the nitrogen-containing bisphosphonates were developed, they proved to be more potent antiresorptive agents that pose less risk of mineralization defects at prescribed doses.

**Alendronate**, approved in 1995, is an oral

nitrogen-containing bisphosphonate that is effective in treating Paget disease.<sup>53</sup> Alendronate is now available in the United States only through special programs (eg, the CVS ProCare Program); the paperwork required to secure this drug is onerous, so the drug is used infrequently. Studies in Paget disease showed that it normalizes the serum alkaline phosphatase level, improves the radiographic appearance, and eases pain in many patients.<sup>54</sup> The dosage is 40 mg daily for 6 months.

**Risedronate**, approved in 1998, is another oral nitrogen-containing bisphosphonate and is comparable to alendronate in efficacy.<sup>55</sup> The dosage is 30 mg daily for 2 months.

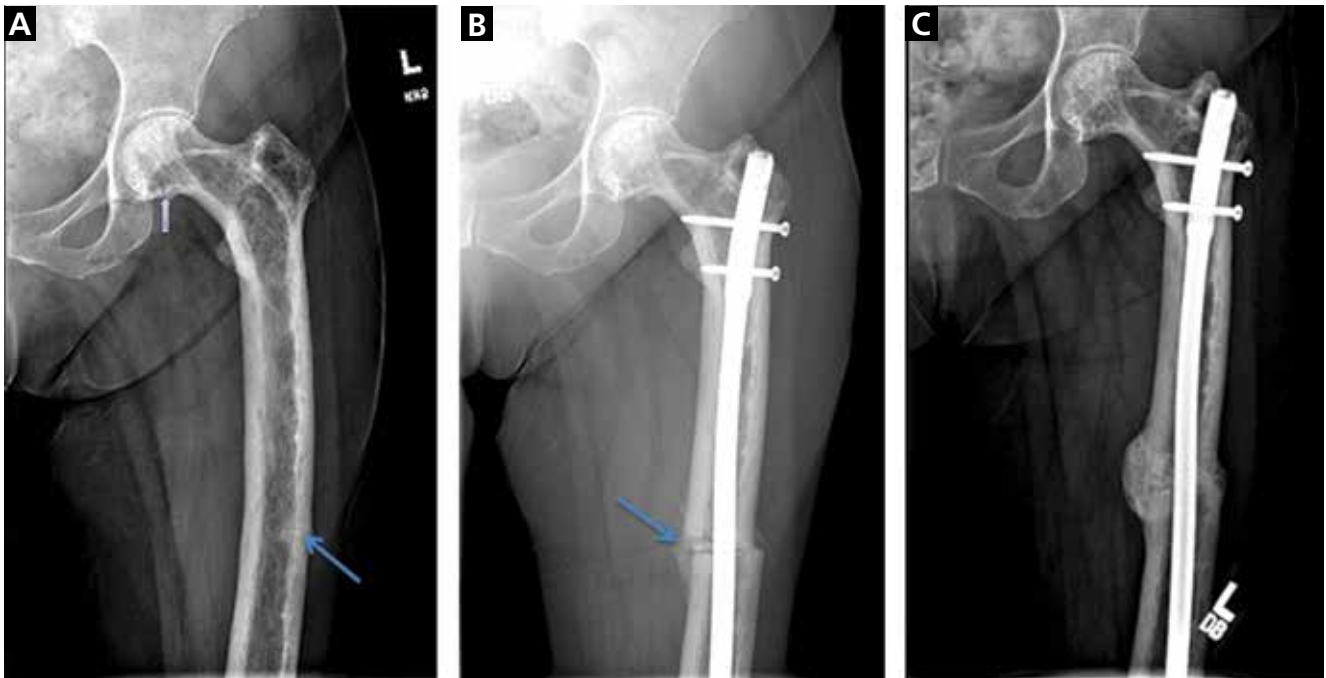
**Tiludronate** is another oral bisphosphonate with a different mechanism of action from the nitrogen-containing bisphosphonates.<sup>56</sup> It is safe, often effective, but less potent than the newer agents.

The oral bisphosphonates are well tolerated, with few side effects other than gastrointestinal distress. As a class, they are poorly absorbed and so must be taken fasting with a full glass of water on rising, after which the patient should remain upright without food or drink for 30 to 60 minutes. This is a nuisance for elderly patients already on multiple medications and thus makes intravenous agents appealing.

## Intravenous bisphosphonates

**Pamidronate** was approved in 1994. Although it does not contain nitrogen, it is quite effective in many patients with Paget disease. There is no consensus around the world on dosing, with regimens ranging from 30 mg to 90 mg or more intravenously in divided doses given over 2 to 4 hours from once a day to once a week. In the United States, 30 mg is given over 4 hours on 3 consecutive days. Resistance to pamidronate has been described; the mechanism is unknown.

**Zoledronic acid** is a nitrogen-containing bisphosphonate. It is given as a single infusion over 15 minutes, and re-treatment may not be necessary for years. A randomized clinical trial in 2005 demonstrated the efficacy of zoledronic acid 5 mg by infusion compared with oral risedronate in the treatment of Paget disease.<sup>57</sup> In observational extension studies lasting as long as 6.5 years, zoledronic acid has been shown to be superior to risedronate in terms



**FIGURE 6.** (A) Plain radiography of the left femur of a woman with Paget disease shows advanced disease, with coarsened trabeculae at the femoral head (short arrow), deformation of the femur, and pseudofractures studding the lateral cortex. The long blue arrow marks the focal area of tenderness described by the patient. Visible is some attendant, reactive sclerosis associated with the pseudofracture. Osteopenia is present in the pelvis. (B) An atraumatic “chalk-stick” fracture occurred at the site of tenderness (arrow). Despite surgical stabilization, pain persisted for more than 6 months after the diaphyseal fracture. (C) Zoledronic acid was prescribed, which resulted in a thickened callus and a return to weight-bearing.

of the proportion of patients experiencing a sustained clinical remission.<sup>58</sup>

While there are many bisphosphonates on the market, an infusion of 5 mg of zoledronic acid seems optimal in most patients who do not have a contraindication or an aversion to intravenous therapy. It tends to normalize the serum alkaline phosphatase level quickly and to leave more patients in sustained biochemical remission than do older bisphosphonates, as noted above. It also tends to be more effective in normalizing the serum alkaline phosphatase level when a patient has used other bisphosphonates in the past or has become resistant to them.

#### **Bisphosphonates reduce bone turnover but do not correct deformities**

In randomized clinical trials, bisphosphonates have been shown to restore bone remodeling to more normal levels, to ease pain from pag-

etic bone, to lower the serum alkaline phosphatase level, and to heal radiographic lesions, but these drugs have not been proven to prevent progression of deformity or to restore the structural integrity of bone (FIGURE 6).

The Paget’s Disease: Randomized Trial of Intensive Versus Symptomatic Management (PRISM), in 1,324 people with Paget disease in the United Kingdom, showed no difference in the incidence of fracture, orthopedic surgery, quality of life, or hearing thresholds over 2 to 5 years in patients treated with bisphosphonates vs those treated symptomatically, despite a significant difference in serum alkaline phosphatase in the two groups ( $P < .001$ ).<sup>59</sup>

In the observational extension study of zoledronic acid described above,<sup>58</sup> three of four fractures occurred in the group treated with zoledronic acid, echoing the findings of the PRISM study.



**Treatment of Paget disease is both safe and effective in easing pain and restoring bone remodeling to more normal levels**

## Adverse effects of bisphosphonates

The more potent the bisphosphonate is as an antiresorptive agent, the more it suppresses normal bone remodeling, which can lead to osteonecrosis of the jaw and to atypical femoral fractures.<sup>60,61</sup> These complications are unusual in patients with Paget disease because the treatment is intermittent. Sometimes a single dose of zoledronic acid or one course of risedronate or alendronate will last for years.

All the nitrogen-containing bisphosphonates, particularly zoledronic acid, may provoke flulike symptoms of fever, arthralgias, and bone pain. This effect is self-limited, resolves in days, and does not tend to recur. Bone pain may be more sustained, but this also passes, and within weeks the antiresorptive process has abated and pagetic bone pain will ease. Atrial fibrillation is not an anticipated complication of treatment with a bisphosphonate.<sup>62</sup> The risk of esophageal cancer is not confirmed at this time.<sup>63</sup> Other rare complications of the bisphosphonates include iritis, acute renal failure, and allergy.

Bisphosphonates are not approved for use in patients with creatinine clearance less than 30 mL/min, or in pregnancy.

## Other treatments

**Calcitonin**, an older agent, can still be useful in easing the pain of Paget disease, healing bone lesions, and reducing the metabolic activity of pagetic bone in patients who cannot receive bisphosphonates. It is given by injection in doses of 50 to 100 IU daily or every other day. Although unlikely to effect a sustained clinical remission, calcitonin remains a safe, well-tolerated, and well-studied medication in Paget disease and is approved for this indication.<sup>64,65</sup>

**Denosumab** has not been formally studied in Paget disease, but a recent case report indicated it was effective.<sup>66</sup>

## A conservative strategy

Guidelines for treating Paget disease have been written at various times in many countries, including Italy (2007),<sup>67</sup> the United Kingdom (2004),<sup>68</sup> Japan (2006),<sup>69</sup> and Canada (2007).<sup>70</sup> Recommendations differ, in part because it is hard to ascertain whether long-term outcomes are improved by treatment, and in part because

the prevalence of Paget disease is decreasing and its severity is lessening.<sup>11,12</sup> Some guidelines are outdated, since they do not include the newer bisphosphonates.

If the natural history of untreated Paget disease involves the gradual evolution over more than 20 years of bowing deformities in the lower limbs, rigidity and overgrowth of the spine, and softening and enlargement of the skull, as described by Sir James Paget, then treatment should be initiated in hopes that it will modify the outcome. We have no lens to better focus this question on the effect of treatment on the natural history of the disease. We have the PRISM study, designed before zoledronic acid was approved and only 2 to 5 years in duration. And we have the epidemiologic data demonstrating that most patients have no symptoms during their lifetime.

We see the crippling bone disease described by Sir James Paget so infrequently today in the United States that we forget the profound morbidity that may attend the skeletal changes of Paget disease that were common in the early 20th century. Once the bones of the skull are overgrown, the limbs are bowed, and the degenerative joint disease is present, no medication can reverse these changes. Then, the integrity of the bone is lost, and the vulnerability to fracture, early osteoarthritis, nerve compression syndromes, and hearing loss persist. Understanding these consequences prompts the recommendation of early treatment in patients with Paget disease, in hopes of mitigating disease progression.

Patients with active Paget disease, documented either by an elevated serum alkaline phosphatase or by a bone scan, should be treated with a bisphosphonate if the disease is found in sites where remodeling of bone may lead to complications. Such sites include the skull, spine, and long bones of the lower extremity. Paget disease of bone in the pelvis tends to give little trouble (**FIGURE 2**) unless it is proximal to a joint, when pain and early arthritis may result. Treatment is safe and, I think, prudent to undertake in any person over age 55 with active disease. To prevent hypocalcemia during treatment, all patients should be repleted with vitamin D and maintained on calcium 1,200 mg daily through diet or supplements with meals.

Throughout the evaluation and treatment, it is important to remember that pain may not emanate from pagetic bone. If medication for Paget disease proves ineffective in the first few months, analgesics, bracing, walking aids, and operative management<sup>71</sup> are adjunctive therapies to improve the functional status of these patients.

It is a remarkable clinical observation that treatment of Paget disease may rapidly reverse neurologic syndromes, resolve the erythema

or warmth overlying active pagetic bone, and diminish the risk of bleeding with surgery. This response to therapy suggests that there is prompt inhibition and apoptosis of the osteoclasts, accompanied by diminished vascularity of bone. Whatever the mechanism, it is worth treating patients who have spinal stenosis, arthritis, and nerve compression syndromes with calcitonin or bisphosphonates before surgical intervention, whenever possible.<sup>34,72</sup> ■

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