Vertebral Fractures

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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 authors' clinical recommendations.

A 72-year-old woman presents with a 2-month history of increasing pain in her lower back, which has not improved with ibuprofen and is causing difficulty with walking and dressing. On questioning, she reports having lost about 5 cm (2 in.) of height since she was a young woman. On examination, there is mild kyphosis in her lower thoracic spine but no point tenderness. A lateral spine radiograph reveals that the L2 vertebra is biconcave in appearance, a finding that is consistent with a vertebral fracture (Fig. 1).

How should this case be managed?

THE CLINICAL PROBLEM

Vertebral fractures — deformities of the vertebral bodies identified with imaging of the lateral spine and characterized according to shape — are the most common manifestation of osteoporosis. Vertebral fractures of the thoracic and lumbar spine account for an estimated 700,000 of the 1.5 million osteoporotic fractures occurring annually in the United States. These fractures are usually identified clinically when a patient presents with back pain, and a spinal radiograph is interpreted as showing a fracture of a vertebral body, most commonly in the thoracolumbar transition zone or midthoracic region. However, in contrast with other fracture types, most vertebral fractures do not come to medical attention at the time of their occurrence. Only one fourth to one third of incident radiographically identified vertebral fractures are clinically diagnosed.

Prevalent radiographic vertebral fractures are modestly associated with back pain and health-related quality of life, the likelihood of back pain, reduced health-related quality of life, and a clinical diagnosis increase with the severity and number of fractures. New radiographic vertebral fractures (e.g., not present on prior radiographs) are associated with increased risks of back pain and back-related disability; the strength of these associations is greater among persons with clinically recognized vertebral fractures. Fracture-related disability may also be greater among patients with lumbar fractures than among those with thoracic fractures.

Vertebral fractures in older adults are associated with an increased risk of death, but this increased risk is due in large part to underlying conditions (e.g., frailty) associated with both vertebral fracture and death. Both prevalent radiographic vertebral fractures and clinical vertebral fractures are also associated with a higher risk of subsequent hip and other fractures; this increase in risk is only partially explained by the lower bone mineral density among patients with vertebral fractures. Thus, the presence of a vertebral fracture has a substantial effect on the risk of subsequent fracture and should influence decisions regarding therapies intended to reduce that risk.
STRATEGIES AND EVIDENCE

EVALUATION
A woman’s first vertebral fracture usually occurs well past menopause. The prevalence and incidence of radiographic vertebral fractures increase with age, with the prevalence among white women rising from 5% to 10% between the ages of 50 and 59 years and to 30% or more at 80 years of age or older. Reported prevalence rates are lower among black women, Asian women, and men. Among older white women without a prevalent vertebral fracture, there is a 0.9% annual risk of incident vertebral fracture among those 65 years of age or older; among those 80 years of age or older, the annual risk is 1.7%. In addition to older age, clinical risk factors for incident vertebral fractures include prior fracture, history of one or more falls, inactivity, current smoking, use of systemic glucocorticoids (the risk increases with increasing cumulative exposure), certain chronic medical conditions (e.g., chronic obstructive pulmonary disease, seropositive rheumatoid arthritis, and Crohn’s disease), and a low body-mass index.

In populations not selected for osteoporosis or fracture risk, height loss (e.g., a loss ≥4 cm since the age of 25 years) has a low sensitivity (31 to 56%) and a positive predictive value (14 to 26%) for the presence of radiographic vertebral fracture but a high negative predictive value (≥86%).

Physical examination may reveal excess sagittal convexity of the thoracic spine (hyperkyphosis, or dowager’s hump), especially among patients with multiple anterior wedge fractures of the thoracic spine. However, severe kyphosis is frequently present in older adults without prevalent radiographic vertebral fractures.

BONE MINERAL DENSITY
Low bone mineral density, as measured with the use of dual-energy x-ray absorptiometry (DEXA), is associated with higher odds of prevalent radiographic vertebral fractures and an increased risk of incident radiographic fractures (odds ratio or hazard ratio for each 1-SD decrease in bone mineral density at the spine or hip, 1.5 to 2.0). Although the prevalence of radiographic vertebral fractures is highest among persons with osteoporosis (defined by a T score at the spine or hip of −2.5 or lower [≥2.5 SD below the mean bone mineral density for healthy young adults]), more than one third of postmenopausal women with prevalent radiographic vertebral fractures have T scores at the spine and hip that are higher than −2.5. The prevalence of radiographic vertebral fractures among women 60 years of age or older with low bone mass (T score at the hip or spine, −1.5 to −2.4) has been reported to range from 14 to 18%

DIAGNOSIS
Although a medical history and an examination may suggest the possibility of a clinical vertebral fracture, the diagnosis must be confirmed with a spinal imaging study. In many cases, lateral chest radiographs ordered for other indications reveal radiographic vertebral fractures, but frequently, such incidental findings are not reported by the radiologist or, if reported, are not acted on by the clinicians responsible for the patient’s care.

Lateral thoracic and lumbar spinal radiographs continue to be the standard for assessment. There is no consensus on the definition of a vertebral fracture, but several qualitative and quantitative methods of adjudication have been developed. The semiquantitative method developed by Genant et al. is widely accepted and is practical for use in the clinical setting. The method uses the qualitative features of vertebral shape and degree of reduction in vertebral height in the anterior, middle, or posterior vertical dimension.
to grade a vertebral body as normal, uncertain regarding fracture, or characterized by a mild, moderate, or severe fracture (see the figure in the Supplementary Appendix, available with the full text of this article at NEJM.org). Appropriate use of this method requires knowledge of developmental deformities (e.g., Scheuermann’s disease [osteochondrosis of vertebral end plates]) and acquired deformities (e.g., osteoarthritis) that do not represent fractures and recognition of features that suggest causes of fractures other than osteoporosis (e.g., expansion of the cortex or lysis of trabeculae or any part of the cortex, findings that are suggestive of cancer). Studies have indicated that the Genant semiquantitative method has good interobserver reliability, concurrent validity (e.g., prevalent fractures are associated with low bone mineral density), and predictive validity (e.g., prevalent fractures predict the risk of incident fractures independently of bone mineral density).16

Assessment for asymptomatic prevalent vertebral fractures can be performed at the time of bone-mineral-density testing with the use of lateral spinal images generated with fan-beam DEXA and appropriate software. The term vertebral-fracture assessment (VFA) denotes densitometric spine imaging from T4 to L4 for the purpose of identifying prevalent vertebral fractures.24 As compared with spinal radiographs, VFA images (Fig. 2) are more likely to produce results that cannot be evaluated (especially when used to assess vertebrae superior to T7)16 but entail much less radiation exposure (3 µSv for VFA vs. 600 µSv for a radiograph of the lateral lumbar spine), substantially reduce the parallax (e.g., projection distortion) often present in vertebrae on radiographs taken with standard cone-beam x-rays, and are more convenient for patients, since imaging can be performed at the same time that bone mineral density is tested. When the Genant semiquantitative method is used with both imaging methods to identify prevalent vertebral fractures, VFA and spinal radiographs have similar intraobserver and interobserver reliability and concurrent validity.19,25 VFA images have a sensitivity and specificity of about 90% for detecting moderate and severe fractures; they are inferior to standard radiographs for detecting mild fractures,19,25 but mild fractures are not as strongly predictive of subsequent fractures as are moderate-to-severe fractures.26

Standard spinal radiographs and VFA are not usually indicated in patients with T scores for bone mineral density that are very low (−2.5 or lower) or high (higher than −1.5), since documentation of vertebral fractures is unlikely to influence management of patient care. However, among postmenopausal women with T scores between −1.5 and −2.4 for whom the benefit of pharmacologic treatment is uncertain, identification of prevalent vertebral fractures may alter management. According to a cost-effectiveness analysis, the use of either spinal radiography or VFA to assess the vertebrae in these women — with bisphosphonates prescribed to those having at least one vertebral fracture — is expected to result in a reduction in the number of fractures for an additional cost (<$50,000 per quality-adjusted life-year gained).27

Other methods of spinal imaging (e.g., computed tomography and magnetic resonance imaging) and radionuclide bone scanning are typically reserved for patients in whom additional information is needed to evaluate the acuity of fractures or to differentiate osteoporotic fractures from pathologic fractures.28

**Treatment**

**Pain Management**

Clinical vertebral fractures may cause pain severe enough to require hospitalization.29 Data from randomized, controlled trials evaluating the efficacy of pain medications in patients with acute vertebral fracture are lacking, but in practice, nonsteroidal antiinflammatory drugs, analgesics (including narcotics and tramadol), transdermal lidocaine, and agents used to relieve neuropathic pain (e.g., tricyclic antidepressants) are commonly used. Although the pain of acute vertebral fracture typically subsides over the course of several weeks, narcotics are often required temporarily to facilitate mobility and avoid prolonged bed rest.30 Small, randomized, placebo-controlled trials suggest that calcitonin (administered by intramuscular injection or as a nasal spray) may modestly reduce pain associated with acute vertebral fracture.31 Teriparatide and bisphosphonates may reduce back pain by preventing new vertebral fractures, but their effectiveness in reducing pain from acute vertebral fractures has not been tested in randomized trials.

**Rehabilitation**

Limited evidence from small, randomized, controlled trials involving patients with clinical vertebral fractures supports the use of therapeutic exer-
exercise programs to reduce pain and improve strength, balance, functional status, and quality of life, but the findings are not consistent across studies.\textsuperscript{32}

Back braces (i.e., spinal orthoses) have been used to treat patients with acute vertebral fractures, but their benefits and harms have not been rigorously evaluated. The results of small, randomized, unblinded trials suggest that use of a rigid back brace during waking hours for 6 weeks or use of a nonrigid back brace for 2 hours per day for 24 weeks may reduce self-reported pain and disability after a clinical vertebral fracture.\textsuperscript{33,34}

**Vertebroplasty and Kyphoplasty**

Vertebral augmentation procedures (vertebroplasty or kyphoplasty) are being performed with increasing frequency in the United States; in 2005, 86 of every 100,000 fee-for-service Medicare beneficiaries underwent vertebroplasty.\textsuperscript{35} Observational studies have reported reductions in pain, disability, and length of hospital stay among patients with acute vertebral fracture who undergo these procedures as compared with those who do not,\textsuperscript{36} but these studies are susceptible to substantial biases.

Two randomized, open-label trials conducted with women who had acute, painful vertebral fractures (mean duration of back pain, 4 to 6 weeks) showed reduced pain and improved physical function among those undergoing kyphoplasty\textsuperscript{37} or vertebroplasty,\textsuperscript{38} but the comparison in each of these trials was usual care rather than a sham procedure. Thus, the observed benefit may have been due to a placebo effect. Another small, randomized trial showed no differences in pain or functional status with vertebroplasty as compared with conservative treatment in patients with painful vertebral fractures that had occurred within the preceding 8 weeks.\textsuperscript{39} Moreover, in two randomized, double-blind trials\textsuperscript{40,41} comparing vertebroplasty with a sham procedure, patients with painful vertebral fractures that had been identified within the preceding 12 months had no benefit from vertebroplasty with respect to pain,

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**Figure 2. Comparison of Densitometric Vertical Fracture Assessment (VFA) with Standard Radiographic Images of the Lateral Thoracic and Lumbar Spine.**

As compared with radiographic images, those obtained with the use of VFA have a lower resolution (the vertebral cortices and end plates are less distinct) and do not capture the thoracic spine well at a level superior to T7 (Panel A, arrow). However, in standard lateral spinal radiographs, projection distortion (parallax) is common (Panels B and C, arrows).
functional disability, or quality of life. The mean duration of symptoms before performance of the procedure was 12 to 13 weeks in one trial and 16 to 20 weeks in the other. Since vertebroplasty and kyphoplasty have been proposed to be most effective for acute fracture pain, analyses were performed in these trials within the subgroup of patients whose pain was of shorter duration, but these analyses did not indicate that vertebroplasty was more beneficial than the sham procedure. However, the power to detect between-group differences was limited.

Vertebroplasty and kyphoplasty are invasive procedures that carry small risks of symptomatic epidural cement leakage, causing nerve-root injury (in 0.4 to 4% of patients) and symptomatic cement pulmonary embolism (in approximately 0.1% of patients). More worrisome is the possibility that the procedures may increase the risk of subsequent vertebral fractures by increasing mechanical load on the vertebrae adjacent to those being treated. No excess risk of subsequent vertebral fractures with vertebroplasty or kyphoplasty has been documented in the randomized trials conducted to date, but these trials were not powered for this outcome.

Calcium and Vitamin D
All current guidelines for the management of osteoporosis recommend adequate intake of calcium (≥1000 mg per day) and vitamin D (≥2600 IU per day). However, no placebo-controlled, randomized trial has shown that there is a reduced risk of incident radiographic or clinical vertebral fractures with the use of calcium alone, vitamin D alone, or calcium combined with vitamin D.

Pharmacotherapy
Pharmacotherapy is indicated to reduce the risk of subsequent fractures in persons with radiographic or clinical vertebral fractures that are not the result of major trauma or cancer, irrespective of the presence or absence of associated symptoms or the bone mineral density T score. Large, randomized, placebo-controlled, double-blind trials conducted in women with postmenopausal osteoporosis (entry criteria included either low bone mineral density or a prevalent radiographic vertebral fracture) have shown the efficacy of several pharmacotherapies in reducing the risk of incident clinical or radiographic vertebral fractures (Table 1). The agents studied included oral bisphosphonates (alendronate, ibandronate, and risedronate), intravenous bisphosphonates (zoledronic acid), selective estrogen-receptor modulators (bazedoxifene, lasofoxifene, and raloxifene), parathyroid hormone, denosumab, strontium ranelate, and calcitonin, although the reported efficacy of calcitonin in reducing new vertebral fractures is questionable. Treatment with bisphosphonates (except ibandronate, for which no data are available), lasofoxifene, strontium, denosumab, or teriparatide has also been shown to reduce the risk of nonvertebral fracture, and there is evidence that alendronate, risedronate, zoledronic acid, or denosumab reduce the risk of hip fracture. Generic alendronate is frequently used as a first-line treatment because of its efficacy in reducing nonvertebral (including hip) and vertebral fractures, its safety profile during 10 years of use, and its relative cost.

Areas of Uncertainty
The value of spinal imaging is uncertain in patients for whom pharmacologic treatment is recommended on the basis of an indication other than vertebral fracture (e.g., bone-mineral-density T score of −2.5 or lower). Information about status with respect to prevalent vertebral fractures may improve the prediction of new vertebral fractures beyond that provided by existing risk-assessment tools, such as the Fracture Risk Assessment Tool (FRAX) from the World Health Organization, but it is unknown whether this is the case for prediction of incident fractures at other skeletal sites and to what extent this information would alter the management of patient care. Among patients with prevalent vertebral fractures or those with osteoporosis, the efficacy of pharmacologic treatment in preventing fractures over a period longer than 3 to 5 years is uncertain, and the risks and benefits of discontinuing treatment for a given period of time are unknown. Additional data from randomized, blinded, well-controlled trials are needed to determine whether vertebral augmentation procedures performed within the first 6 weeks after a disabling vertebral fracture are efficacious and safe. Trials are also warranted for patients with clinical vertebral fractures to determine the effect of spinal orthoses and exercise programs on long-term pain, mobility, functional status, and quality of life.
Table 1. Medications for Reducing the Risk of Fracture in Postmenopausal Women with Prevalent Vertebral Fractures.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Fracture Risk Reduction</th>
<th>Side Effects or Risks</th>
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<tbody>
<tr>
<td>Bisphosphonates</td>
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<tr>
<td>Alendronate†</td>
<td>70 mg orally, once per wk</td>
<td>Vertebral, nonvertebral, hip</td>
<td>Upper gastrointestinal irritation is common, esophageal ulcer and bone pain are uncommon, and osteonecrosis of the jaw and atypical fractures of the femoral shaft are rare</td>
</tr>
<tr>
<td>Ibandronate†</td>
<td>150 mg orally, once per mo</td>
<td>Vertebral with oral administration, 3 mg intravenous, every 3 mo</td>
<td>With oral administration, upper gastrointestinal irritation is common, esophageal ulcer and bone pain are uncommon, and osteonecrosis of the jaw and atypical fractures of the femoral shaft are rare; with intravenous administration, influenza-like symptoms are common, hypocalcemia is uncommon, and osteonecrosis of the jaw and atypical fractures of the femoral shaft are rare</td>
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<tr>
<td>Risedronate†</td>
<td>35 mg orally, once per wk, or 150 mg orally, once per mo</td>
<td>Vertebral, nonvertebral, hip</td>
<td>Upper gastrointestinal irritation is common, esophageal ulcer and bone pain are uncommon, and osteonecrosis of the jaw and atypical fractures of the femoral shaft are rare</td>
</tr>
<tr>
<td>Zoledronic acid†</td>
<td>5 mg intravenously, once per year</td>
<td>Vertebral, nonvertebral, hip</td>
<td>Bone pain with first dose and influenza-like symptoms are common, hypocalcemia is uncommon, and osteonecrosis of the jaw and atypical fractures of the femoral shaft are rare</td>
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<tr>
<td>SERMs</td>
<td></td>
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<tr>
<td>Bazedoxifene‡</td>
<td>20 mg orally, once per day</td>
<td>Vertebral</td>
<td>Leg cramps and hot flashes are common; uterine polyps and deep-vein thrombosis are uncommon</td>
</tr>
<tr>
<td>Lasofoxifene‡</td>
<td>0.5 mg orally, once per day</td>
<td>Vertebral, nonvertebral</td>
<td>Leg cramps and hot flashes are common; uterine polyps and deep-vein thrombosis are uncommon</td>
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<tr>
<td>Raloxifene‡</td>
<td>60 mg orally, once per day</td>
<td>Vertebral</td>
<td>Leg cramps and hot flashes are common; uterine polyps and deep-vein thrombosis are uncommon</td>
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<td>PTH</td>
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<tr>
<td>Recombinant human PTH(1–84)†‡</td>
<td>100 μg subcutaneously, once per day</td>
<td>Vertebral</td>
<td>Nausea, arthralgia, leg cramps, hypercalcemia, and hypercalciuria are common; hyperuricemia and hypotension are uncommon</td>
</tr>
<tr>
<td>Teriparatide (PTH[1–34])†‡</td>
<td>20 μg subcutaneously, once per day</td>
<td>Vertebral, nonvertebral</td>
<td>Nausea, arthralgia, leg cramps, hypercalcemia, and hypercalciuria are common; hyperuricemia and hypotension are uncommon</td>
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<tr>
<td>RANKL inhibitor</td>
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<tr>
<td>Denosumab†</td>
<td>60 mg subcutaneously, every 6 mo</td>
<td>Vertebral, nonvertebral, hip</td>
<td>Eczema, nausea, and injection-site reactions are common; osteonecrosis of the jaw is rare</td>
</tr>
<tr>
<td>Calcitonin‡</td>
<td>100–200 IU nasally or subcutaneously, once per day</td>
<td>Vertebral</td>
<td>With nasal administration, nasal stuffiness is common and nausea is uncommon; with subcutaneous administration, nausea, injection site-reactions, and flushing of hands or face are common</td>
</tr>
<tr>
<td>Other</td>
<td></td>
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<tr>
<td>Strontium ranelate‡</td>
<td>2 g orally, once per day</td>
<td>Vertebral, nonvertebral</td>
<td>Diarrhea, nausea, eczema, and headache are common; elevated serum levels of creatine kinase are uncommon</td>
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</table>

* All agents have been evaluated in randomized, placebo-controlled trials with a fracture outcome as the primary end point. The proportion of participants with prevalent vertebral fractures in these trials ranged from 19 to 100%. All participants in these trials, including those in the placebo group, received supplemental calcium and vitamin D. PTH denotes parathyroid hormone, RANKL receptor activator of nuclear factor κB ligand, and SERM selective estrogen-receptor modulator.

† This agent was approved by the Food and Drug Administration (FDA) for the treatment of postmenopausal osteoporosis.

‡ This drug has not been approved by the FDA but has been approved for use in the European Union.
G U I D E L I N E S  F R O M  P R O F E S S I O N A L  S O C I E T I E S

The International Society for Clinical Densitometry has published guidelines for the assessment of vertebral fractures.\textsuperscript{16} Several organizations, including the National Osteoporosis Foundation, the European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis, and the American College of Physicians,\textsuperscript{99-101} have published guidelines for the diagnosis and treatment of osteoporosis that address the management implications of identifying vertebral fractures and the effectiveness of pharmacologic agents in fracture prevention. The recommendations in this article are generally concordant with these guidelines.

C O N C L U S I O N S  A N D  R E C O M M E N D A T I O N S

The history and examination of the patient in the vignette suggest a clinical vertebral fracture, but the diagnosis must be confirmed with an imaging study of the spine. The identification of a vertebral fracture indicates a diagnosis of osteoporosis, regardless of the patient’s bone-mineral-density T score. Relieving pain and preserving mobility should be immediate goals that may require short-term narcotic therapy. Although there are uncertainties about the effect of therapeutic exercise, we would recommend a targeted physical therapy program that incorporates postural retraining and exercises to improve the strength of back extensor musculature and mobility.

Since vertebral fractures are associated with an increased risk of future fractures, the long-term goal should be reducing the risk of subsequent fractures. We recommend a calcium intake of 1000 to 1200 mg per day and a vitamin D intake of 600 to 800 IU per day (through diet, supplements, or both), although the benefit of this approach in reducing the risk of subsequent vertebral fractures is uncertain. Although several medications reduce the risk of new vertebral fractures, we recommend the initiation of treatment with generic alendronate, considering its efficacy in reducing incident fractures, including hip fracture, and its safety and relatively low cost.

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

R E F E R E N C E S

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