Recently there has been concern about two potential side effects associated with bisphosphonate use. The first is osteonecrosis of the jaw (ONJ). ONJ usually follows a dental procedure in which bone is exposed (extractions or dental implants). It is presumed that the exposed bone becomes infected and dies. It is not uncommon among cancer victims with multiple myeloma or patients receiving high doses of bisphosphonates for skeletal metastases, but is rare among persons with osteoporosis on usual doses of bisphosphonates. The second side effect is called atypical femur fracture. These are unusual fractures that occur distal to the lesser trochanter and anywhere along the femoral shaft. They are often preceded by pain in the lateral thigh or groin that can be present for weeks or months before the fracture. The fractures occur with trivial trauma, sometimes completely spontaneously, and are primarily transverse, with a medial break when complete and minimally comminuted. A localized periosteal reaction, consistent with a stress fracture, is often seen in the lateral cortex **(Fig. 425-10)**. The overall risk is low (suggested to be about one-one hundredth to one-tenth that of hip fracture) but appears to increase in incidence with long-term use of bisphosphonates. Although the fractures may be bisphosphonate related in many individuals, they clearly occur in patients with no prior bisphosphonate exposure. When complete, they require surgical fixation and may be difficult to heal. Anabolic medication may accelerate healing of these fractures in some patients, and surgery can sometimes be avoided. Patients initiating bisphosphonates need to be warned that if they develop thigh or groin pain they must notify their physician. Routine x-rays will sometimes pick up cortical thickening or even a stress fracture, but more commonly MRI or technetium bone scan is required. The presence of an abnormality requires at minimum a period of modified weight bearing and may need prophylactic rodding of the femur. It is important to realize that these fractures may be bilateral, and when an abnormality is found, the other femur should be investigated.

MODE OF ACTION Bisphosphonates are structurally related to pyrophosphates, compounds that are incorporated into bone matrix. Bisphosphonates specifically impair osteoclast function and reduce osteoclast number, in part by inducing apoptosis. Recent evidence suggests that the nitrogen-containing bisphosphonates also inhibit protein prenylation, one of the end products in the mevalonic acid pathway, by inhibiting the enzyme farnesyl pyrophosphate synthase. This effect disrupts intracellular protein trafficking and ultimately may lead to apoptosis. Some bisphosphonates have very long retention in the skeleton and may exert long-term effects. The consequences of this, if any, are unknown.

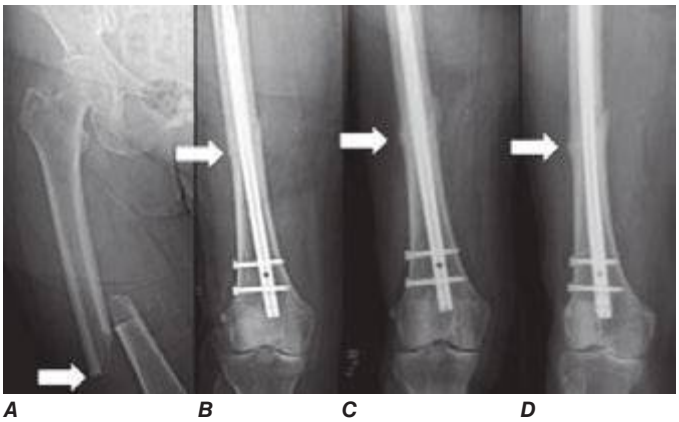

FIGURE 425-10 An atypical femur fracture (AFF) of the femoral diaphysis. *A.* Note the transverse fracture line in the lateral cortex that becomes oblique as it progresses medially across the femur (*white arrow*). ***B.*** On radiograph obtained immediately after intramedullary rod placement, a small area of periosteal thickening of the lateral cortex is visible (*white arrow*). ***C.*** On radiograph obtained at 6 weeks, note callus formation of the fracture site (*white arrow*). ***D.*** On radiograph obtained at 3 months, there is a mature callus that has failed to bridge the cortical gap (*white arrow*). Note the localized periosteal and/or endosteal thickening of the lateral cortex at the fracture site (*white arrow*). *(From E Shane et al: J Bone Min Res 29:1-23, 2014. Courtesy of Fergus McKiernan.)*

Calcitonin Calcitonin is a polypeptide hormone produced by the thyroid gland **(Chap. 424)**. Its physiologic role is unclear because no skeletal disease has been described in association with calcitonin deficiency or excess. Calcitonin preparations are approved by the FDA for Paget's disease, hypercalcemia, and osteoporosis in women >5 years past menopause. Concerns have been raised about an increase in the incidence of cancer associated with calcitonin use. Initially, the cancer noted was of the prostate, but an analysis of all data suggested a more general increase in cancer risk. In Europe, the European Medicines Agency (EMA) has removed the osteoporosis indication, and an FDA Advisory Committee has voted for a similar change in the United States.

Injectable calcitonin produces small increments in bone mass of the lumbar spine. However, difficulty of administration and frequent reactions, including nausea and facial flushing, make general use limited. A nasal spray containing calcitonin (200 IU/d) is available for treatment of osteoporosis in postmenopausal women. One study suggests that nasal calcitonin produces small increments in bone mass and a small reduction in new vertebral fractures in calcitonin-treated patients versus those on calcium alone. There has been no proven effectiveness against nonvertebral fractures.

Calcitonin is not indicated for prevention of osteoporosis and is not sufficiently potent to prevent bone loss in early postmenopausal women. Calcitonin might have an analgesic effect on bone pain, both in the subcutaneous and possibly the nasal form.

MODE OF ACTION Calcitonin suppresses osteoclast activity by direct action on the osteoclast calcitonin receptor. Osteoclasts exposed to calcitonin cannot maintain their active ruffled border, which normally maintains close contact with underlying bone.

Denosumab A novel agent that was given twice yearly by SC administration in a randomized controlled trial in postmenopausal women with osteoporosis has been shown to increase BMD in the spine, hip, and forearm and reduce vertebral, hip, and nonvertebral fractures over a 3-year period by 70, 40, and 20%, respectively **(Fig. 425-11)**. Other clinical trials indicate ability to increase bone mass in postmenopausal women with low bone mass (above osteoporosis range) and in postmenopausal women with breast cancer treated with hormonal agents. Furthermore, a study of men with prostate cancer treated with gonadotropin-releasing hormone (GnRH) agonist therapy indicated the ability of denosumab to improve bone mass and reduce vertebral fracture occurrence. Denosumab was approved by the FDA in 2010 for the treatment of postmenopausal women who have a high risk for osteoporotic fractures, including those with a history of fracture or multiple risk factors for fracture, and those who have failed or are intolerant to other osteoporosis therapy. Denosumab is also approved for the treatment of osteoporosis in men at high risk, men with prostate cancer on GnRH agonist therapy, and women with breast cancer on aromatase inhibitor therapy.

MODE OF ACTION Denosumab is a fully human monoclonal antibody to RANKL, the final common effector of osteoclast formation, activity, and survival. Denosumab binds to RANKL, inhibiting its ability to initiate formation of mature osteoclasts from osteoclast precursors and to bring mature osteoclasts to the bone surface and initiate bone resorption. Denosumab also plays a role in reducing the survival of the osteoclast. Through these actions on the osteoclast, denosumab induces potent antiresorptive action, as assessed biochemically and histomorphometrically, and may contribute to the occurrence of ONJ. Atypical femur fractures have also been noted. Serious adverse reactions include hypocalcemia, skin infections (usually cellulitis of the lower extremity), and dermatologic reactions such as dermatitis, rashes, and eczema. The effects of denosumab are rapidly reversible.