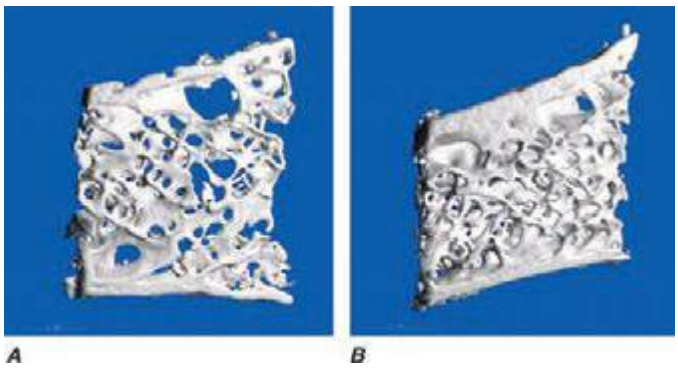

FIGURE 425-13 Effect of parathyroid hormone (PTH) treatment on bone microarchitecture. Paired biopsy specimens from a 64-year-old woman before (***A***) and after (***B***) treatment with PTH. *(From DW Dempster et al: J Bone Miner Res 16:1846, 2001.)*

PTH might be effective when used intermittently. Cost also may be a limiting factor. In some settings, the effect of PTH might be enhanced by combination with an antiresorptive agent. This might be particularly important in patients who have been treated previously with bisphosphonate medications.

MODE OF ACTION Exogenously administered PTH appears to have direct actions on osteoblast activity, with biochemical and histomorphometric evidence of de novo bone formation early in response to PTH, before activation of bone resorption. Subsequently, PTH activates bone remodeling but still appears to favor bone formation over bone resorption. PTH stimulates Wnt signaling, IGF-I, and collagen production and appears to increase osteoblast number by stimulating replication, enhancing osteoblast recruitment, and inhibiting apoptosis. Unlike all other treatments, PTH produces a true increase in bone tissue and an apparent restoration of bone microarchitecture **(Fig. 425-13)**.

Fluoride Fluoride has been available for many years and is a potent stimulator of osteoprogenitor cells when studied in vitro. It has been used in multiple osteoporosis studies with conflicting results, in part because of the use of varying doses and preparations. Despite increments in bone mass of up to 10%, there are no consistent effects of fluoride on vertebral or nonvertebral fracture; the latter may actually increase when high doses of fluoride are used. Fluoride remains an experimental agent despite its long history and multiple studies.

Strontium Ranelate Strontium ranelate is approved in several European countries for the treatment of osteoporosis. It increases bone mass throughout the skeleton; in clinical trials, the drug reduced the risk of vertebral fractures by 37% and that of nonvertebral fractures by 14%. It appears to be modestly antiresorptive while at the same time not causing as much of a decrease in bone formation (measured biochemically). Strontium is incorporated into hydroxyapatite, replacing calcium, a feature that might explain some of its fracture benefits. Small increased risks of venous thrombosis, sometimes severe dermatologic reactions, seizures, and abnormal cognition have been seen and require further study. An increase in risk of cardiovascular disease has also been associated with use of strontium, such that the EMA has restricted its use at present.

Other Potential Anabolic Agents Several small studies of growth hormone (GH), alone or in combination with other agents, have not shown consistent or substantial positive effects on skeletal mass. Many of these studies have been relatively short term, and the effects of GH, growth hormone–releasing hormone, and the IGFs are still under investigation. Anabolic steroids, mostly derivatives of testosterone, act primarily as antiresorptive agents to reduce bone turnover but also may stimulate osteoblastic activity. Effects on bone mass remain unclear but appear weak in general, and use is limited by masculinizing side effects. Several observational studies suggested that the statin drugs, used to treat hypercholesterolemia, may be associated with increased bone mass and reduced fractures, but conclusions from clinical trials have been largely negative. Early studies with sclerostin antibodies, which inhibit sclerostin, activate Wnt, and might be highly anabolic to bone, are under development. Odanacatib is a mixed antiresorptive, partial bone formation stimulator that is currently in the late stages of development.

NONPHARMACOLOGIC APPROACHES

In some early studies, protective pads worn around the outer thigh, which cover the trochanteric region of the hip, were able to prevent hip fractures in elderly residents in nursing homes. Randomized controlled trials of hip protectors have been unable to confirm these early findings. Therefore, the efficacy of hip protectors remains controversial at this time.

Kyphoplasty and *vertebroplasty* are also useful nonpharmacologic approaches for the treatment of painful vertebral fractures. However, no long-term data are available.

TREATMENT MONITORING

There are currently no well-accepted guidelines for monitoring treatment of osteoporosis. Because most osteoporosis treatments produce small or moderate bone mass increments on average, it is reasonable to consider BMD as a monitoring tool. Changes must exceed ~4% in the spine and 6% in the hip to be considered significant in any individual. The hip is the preferred site due to larger surface area and greater reproducibility. Medication-induced increments may require several years to produce changes of this magnitude (if they do at all). Consequently, it can be argued that BMD should be repeated at intervals >2 years. Only significant BMD reductions should prompt a change in medical regimen, because it is expected that many individuals will not show responses greater than the detection limits of the current measurement techniques.

Biochemical markers of bone turnover may prove useful for treatment monitoring, but little hard evidence currently supports this concept; it remains unclear which endpoint is most useful. If bone turnover markers are used, a determination should be made before therapy is started and repeated ≥4 months after therapy is initiated. In general, a change in bone turnover markers must be 30–40% lower than the baseline to be significant because of the biologic and technical variability in these tests. A positive change in biochemical markers and/or bone density can be useful to help patients adhere to treatment regimens.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Osteoporotic fractures are a well-characterized consequence of the hypercortisolism associated with Cushing's syndrome. However, the therapeutic use of glucocorticoids is by far the most common form of glucocorticoid-induced osteoporosis. Glucocorticoids are used widely in the treatment of a variety of disorders, including chronic lung disorders, rheumatoid arthritis and other connective tissue diseases, inflammatory bowel disease, and after transplantation. Osteoporosis and related fractures are serious side effects of chronic glucocorticoid therapy. Because the effects of glucocorticoids on the skeleton are often superimposed on the consequences of aging and menopause, it is not surprising that women and the elderly are most frequently affected. The skeletal response to steroids is remarkably heterogeneous, however, and even young, growing individuals treated with glucocorticoids can present with fractures.

The risk of fractures depends on the dose and duration of glucocorticoid therapy, although recent data suggest that there may be no completely safe dose. Bone loss is more rapid during the early months of treatment, and trabecular bone is affected more severely than cortical bone. As a result, fractures have been shown to increase within 3 months of steroid treatment. There is an increase in fracture risk in both the axial skeleton and the appendicular skeleton, including risk of hip fracture. Bone loss can occur with any route of steroid administration, including high-dose inhaled glucocorticoids and intraarticular