UPDATE
Update in Osteoporosis and Metabolic Bone Disorders

Dolores Shoback
Endocrine Research Unit, San Francisco Department of Veterans Affairs Medical Center, and Department of Medicine, University of California, San Francisco 94121

Considerable progress has been made in the development and testing of agents to treat osteoporosis. Most impressive are reports on new antiresorptive agents—both bisphosphonates (ibandronate and zoledronic acid) and monoclonal antibodies (MAbs) (denosumab) directed against receptor activator of nuclear factor κB-ligand, a key molecule in the control of commitment and activation of osteoclasts. Bisphosphonates promise convenience and potency at slowing bone loss, whereas denosumab offers powerful suppression of resorption and rapid offset of action. Attention is also shifting from the osteoclast as a target for new therapies to the osteoblast and the osteocyte, with its complex network within the depths of bone. Wnt signaling through the frizzled receptor and its coreceptor, the low-density lipoprotein receptor related protein-5, appears from both molecular and in vivo evidence to be a pivotal pathway for modulating osteoblastic activity, bone formation, and bone strength. The recently identified product of the SOST gene or sclerostin has also been shown to block Wnt signaling. Sclerostin is produced by the osteocytes buried in the bone and is a new target to treat bone loss. Clinical trial reports indicate that the calcimimetic cinacalcet can effectively treat PTH hypersecretion due to primary and secondary hyperparathyroidism and parathyroid carcinoma. Lastly, it is now recognized that the matrix protein dentin matrix protein-1 enhances the release of the phosphate-regulating factor fibroblast growth factor 23 and that mutations in dentin matrix protein-1 play a causative role in a form of hypophosphatemic rickets. (J Clin Endocrinol Metab 92: 747–753, 2007)

INSIGHTS INTO THE actions of hormones and cytokines in bone cells and their effects on skeletal mass and strength continue to develop at a brisk pace, and the past 2 yr have been no exception (1, 2). Just when it appeared that the field of therapies for postmenopausal osteoporosis had reached maturity, pivotal trial data on the efficacy of a monthly oral and quarterly iv infusion of the bisphosphonate ibandronate were released, and the drug was approved by the United States Food and Drug Administration (FDA) (3–5). Data from another large clinical trial recently demonstrated the efficacy of annual infusions of the iv bisphosphonate zoledronic acid in preventing osteoporotic fractures in patients (6). Other studies suggest that denosumab offers powerful suppression of resorption and rapid offset of action. Attention is also shifting from the osteoclast as a target for new therapies to the osteoblast and the osteocyte, with its complex network within the depths of bone. Wnt signaling through the frizzled receptor and its coreceptor, the low-density lipoprotein receptor related protein-5, appears from both molecular and in vivo evidence to be a pivotal pathway for modulating osteoblastic activity, bone formation, and bone strength. The recently identified product of the SOST gene or sclerostin has also been shown to block Wnt signaling. Sclerostin is produced by the osteocytes buried in the bone and is a new target to treat bone loss. Clinical trial reports indicate that the calcimimetic cinacalcet can effectively treat PTH hypersecretion due to primary and secondary hyperparathyroidism and parathyroid carcinoma. Lastly, it is now recognized that the matrix protein dentin matrix protein-1 enhances the release of the phosphate-regulating factor fibroblast growth factor 23 and that mutations in dentin matrix protein-1 play a causative role in a form of hypophosphatemic rickets. (J Clin Endocrinol Metab 92: 747–753, 2007)

Abbreviations: BMD, Bone mineral density; CaR, calcium-sensing receptor; Cl, confidence interval; Dkk, Dickkopf; DMP-1, dentin matrix protein-1; 1,25 D, 1,25 dihydroxyvitamin D; FGF-23, fibroblast growth factor 23; 25 OH D, 25 hydroxyvitamin D; LRP-5, low-density lipoprotein receptor related protein 5; MAb, monoclonal antibody; ONJ, osteonecrosis of the jaws; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor κB; RANK-L, RANK ligand; RR, relative risk; SERM, selective estrogen response modulator.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.
in mineralization and in the control of FGF-23 secretion by bone cells.

**Pathophysiology of osteoporosis**

An imbalance between osteoclast-mediated bone resorption and bone formation remains a key means to understanding and treating postmenopausal osteoporosis (1, 2). The RANK-L/RANK/OPG pathway mediates the production and activity of cells in the osteoclast lineage (Fig. 1). RANK-L, a member of the TNF superfamily, is produced by bone marrow stromal cells and lining cells of the osteoblastic lineage. It interacts with RANK, a TNF receptor family member, on cells of the macrophage/monocyte lineage as well as mature osteoclasts. The soluble protein OPG, released by osteoblasts into the microenvironment, interrupts the interaction between RANK-L and RANK in the role of OPG as a decoy receptor. Knockout and transgenic mouse models, as well as rare cases of human mutations in the genes encoding the members of this pathway, further establish the essential features of this paradigm for the control of osteoclastogenesis and bone resorption.

The spotlight for understanding and treating bone loss is, however, beginning to shift from osteoclasts to bone-forming osteoblasts and the complex network of osteocytes buried deep in the bone matrix. Numerous studies over the last few years have provided important insights into the role of Wnt signaling in controlling osteoblast differentiation, the accrual of bone mass, and bone loss (1, 2, 19, 20) (Fig. 2). As it is currently understood, one of the Wnt proteins serves as a ligand for the receptor frizzled (fzl), whose co-receptor is the low-density lipoprotein receptor related protein 5 (LRP-5) in osteoblasts. Together fzl and LRP-5 transduce Wnt signals. The soluble protein Dickkopf (Dkk) antagonizes this signaling, as does the osteocyte-derived product of the SOST gene sclerostin (20). After a series of biochemical events within the cell, Wnt signaling leads to stabilization of β-catenin. β-Catenin accumulation promotes transcriptional events that increase osteoblast number and activity and ultimately bone formation.

**Therapies for osteoporosis**

**Antiresorptive agents: bisphosphonates**

**Ibandronate.** This potent aminobisphosphonate has been studied in a variety of dosing regimens. In a study called the MOBILE (Monthly Oral Ibandronate in Ladies) trial, responses in bone mineral density (BMD) and bone turnover markers in postmenopausal women with low bone mass were compared on daily and monthly dosing schedules. The analysis of responses after 1 yr of treatment showed noninferiority for the three-monthly regimens and superiority in the responses in the cohort of women dosed at monthly (150 mg) compared with daily (2.5 mg) schedules (3). The same results were confirmed in the second year of this trial (4). Another trial with ibandronate called DIVA (Dosing Intravenous Administration) showed that BMD responses in patients on the two iv regimens (2 mg every 2 months and 3 mg every 3 months) compared favorably to daily (2.5 mg) oral dosing (5). This latter daily regimen of ibandronate was shown previously to reduce vertebral fracture risk, when compared with placebo, in the phase 3 fracture trial called BONE (Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe), which was reported in 2004 (21). The two most recent trials noted above (MOBILE and DIVA) supported the approval of ibandronate as a 150-mg tablet for monthly use (3, 4) and a 3-mg iv preparation (5) for the treatment of postmenopausal osteoporosis.

**Alendronate.** The Fracture Intervention Trial (FIT) established the efficacy of alendronate in the prevention of frac-

---

**Fig. 1.** RANK-L/RANK/OPG pathway for regulating osteoclastogenesis and osteoclast function. Precursor cells from the macrophage/monocyte lineage reach the bone marrow microenvironment where the growth factor macrophage colony-stimulating factor (M-CSF) released by osteoblasts and stromal cells interacts with the receptor for M-CSF, c-fms on osteoclastic precursors. M-CSF, in concert with RANK-L produced by osteoblasts and bone marrow stromal cells, induces these precursor cells to begin differentiation toward fully mature and functional osteoclasts containing multiple nuclei and the ruffled border as shown. The interaction between RANK-L, expressed on cells in the osteoblastic/stromal cell population, and RANK, expressed on osteoclast precursors and osteoclasts during differentiation, maintain the life span and promote the bone-resorbing capabilities of active osteoclasts. The soluble decoy receptor OPG released by osteoblasts antagonizes the interaction between RANK-L and RANK and inhibits osteoclast formation. The balance between signaling generated via the interaction of RANK-L and RANK and its blockade by circulating OPG balance the rate of osteoclast formation and thereby bone resorption. [Modified with permission from L. G. Raisz: *J Clin Invest* 115: 3318–3325, 2005 (1).]
features in postmenopausal osteoporosis nearly a decade ago (22, 23). FIT included approximately 4–5 yr of treatment with alendronate or placebo. Subsequently, women who had been treated with alendronate for 3–4.5 yr were randomized to either daily alendronate or placebo for an additional 5 yr in FLEX (the FIT Long-term Extension) (24). BMD, biochemical markers of bone turnover, and fractures were assessed in FLEX. There were modest decreases in BMD by dual energy x-ray absorptiometry at the total hip (−2.4%) and spine (−3.7%) in patients switched to placebo after 5 yr of therapy with alendronate in FLEX. When the cumulative incidence of clinical vertebral fractures during FLEX was compared, there was a significant decrease in the relative risk (RR) of clinical vertebral fractures [RR, 0.45; 95% confidence interval (CI), 0.24–0.85] in women treated with alendronate for nearly 10 yr, compared with 3–4.5 yr of alendronate followed by placebo for 5 yr. The incidences of morphometric vertebral, clinical nonvertebral, and hip fractures were not statistically different between placebo- vs. alendronate-treated patients during FLEX (24).

Important safety data from bone biopsies in postmenopausal women who, after long-term alendronate therapy in FLEX were treated with either alendronate or placebo, have also been presented (n = 9 per group). These findings were compared with premenopausal (n = 34) and historical osteoporotic controls (n = 90). Dual-labels of tetracycline were evident in all specimens, supporting the idea that skeletal turnover was not completely suppressed (24). Trabecular microarchitecture was preserved, and other trabecular parameters were not significantly different from controls. Although the numbers of biopsies were small, these are key safety data from patients with the longest record of exposure to alendronate thus far.

Zoledronic acid. Preliminary results were reported in 2006 (6) on the antifracture efficacy of the iv aminobisphosphonate zoledronic acid from a study of 7736 women with postmenopausal osteoporosis. Women treated for 3 yr with zoledronic acid (5 mg/yr), along with supplemental calcium (1000–1500 mg/d) and vitamin D (400–1200 IU/d), showed significantly reduced risks of morphometric vertebral (by 70%), nonvertebral (by 25%), and hip fractures (by 40%), compared with placebo. This study did not assess how long annual infusions of iv zoledronic acid remained active in vivo, in terms of suppressing bone turnover, although this is an important issue for clinicians. Adverse events included mild reversible renal impairment. There was no difference in the number of cases of osteonecrosis of the jaws (ONJ) in placebo- vs. zoledronic acid-treated patients (two vs. one patients, respectively). If this agent receives FDA approval, it will represent an exceptionally convenient therapy for patients with osteoporosis.

Risedronate. Risedronate has been FDA-approved for treatment of osteoporosis in men. Recent data from a 1-yr open-label study of men with primary or secondary osteoporosis...
showed increases in BMD at the lumbar spine, femoral neck, and total hip that were significantly greater than placebo and a 60% reduction in new vertebral fractures vs. the control group \( (P = 0.028) \) (25).

**Safety concerns with bisphosphonates.** Because of the long half-life of potent aminobisphosphonates in bone matrix, concerns have heightened about the possibility of oversuppressing bone turnover with these agents. Theoretically, this could lead to failure to repair microdamage to bone and poor healing of fractures. These concerns were brought to the forefront by the report of Ovdina et al. (26) of nine patients receiving alendronate. These patients presented with fractures at unusual sites (sacrum, femoral shaft, proximal femur) that were slow to heal. Bone biopsies in these patients showed suppressed bone formation parameters and reduced osteoblast surfaces, and there was an absence of double-tetracycline labels—compatible with low bone turnover. Although in several of the cases in this series there were other contributors to low turnover (glucocorticoids and concomitant estrogen and alendronate therapy), this report heightened awareness of the ramifications of oversuppressing remodeling by potent bisphosphonates.

Several case reports and clinical series have documented a newly appreciated oral complication associated with aminobisphosphonate therapy—ONJ. Approximately 94% of cases have been seen with iv bisphosphonate therapy, typically in patients with cancer (27). The condition is characterized by typically painful sites of exposed bone in the mandible or maxilla that do not resolve after 8–12 wk in patients who have not received radiation therapy to the jaw (27–29). Infections may also accompany ONJ. Longer duration and potency of iv bisphosphonate use, prior dentoalveolar surgery, preexisting oral inflammatory disease, age, underlying cancer, chemotherapy, and the presence of osteopenia or osteoporosis at time of diagnosis have been identified as precipitating factors for the condition. There have been 15, one, and one cases of ONJ in patients with osteoporosis treated with oral alendronate, risedronate, and ibandronate, respectively (27). Only 15 of the 368 cases of ONJ reviewed by Woo et al. (27) had a primary diagnosis of osteoporosis. Thus, estimates are that the risk of ONJ in patients with osteoporosis is very rare (30).

The pathogenesis of ONJ is poorly understood. Management strategies continue to evolve and are largely empirical, based on the personal experience of expert oral and maxillofacial surgeons (28, 29). Continued dental surveillance of patients being treated with potent aminobisphosphonates is indicated, package labeling for the aminobisphosphonates now reflect this possible complication, and additional studies are needed to improve our understanding of this potentially devastating condition.

**Antiresorptive therapy: selective estrogen response modulators (SERMs).** Several studies assessing the advantages and or disadvantages of SERM therapy on other than skeletal endpoints in postmenopausal women have recently been published. In 2004, the CORE (Continuing Outcomes Relevant to Evista) trial reported that postmenopausal women treated with raloxifene for 8 yr demonstrated a 66% reduction in the risk of invasive breast cancer compared with placebo (31). The RR of thromboembolism in raloxifene- vs. placebo-treated women in CORE was 2.17 (95% CI, 0.83–5.70) (31).

Because tamoxifen is approved for the prevention of breast cancer and studies with raloxifene have been shown decrements in new cases of breast cancer, the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) was designed to examine in a randomized, double-blind trial the efficacy of daily tamofoxen (20 mg) vs. raloxifene (60 mg) for a maximum of 5 yr to prevent breast cancer (32). A total of 19,747 postmenopausal women, deemed at high risk for breast cancer based on the Gail model, were randomized to one of these two SERMs. After a mean follow-up of 3.9 yr, there was no significant difference between tamoxifen and raloxifene in the rate of invasive breast cancers (32). Similar numbers of noninvasive breast or other invasive cancers, ischemic heart disease events, stroke, osteoporotic fractures, and deaths were seen in both cohorts of women. There were, however, fewer occurrences of thromboembolic events (−30% less) and either cataracts or cataract surgeries (−20% less for each) in raloxifene- vs. tamoxifen-treated women.

Shortly after this report came the findings of the RUTH (Ralofixene Use for the Heart) trial (33). This study randomized 10,101 postmenopausal women (mean age, 67.5 yr) with coronary heart disease or risk factors for it to receive raloxifene (60 mg/d) or placebo. After 5.6 yr of treatment, raloxifene did not significantly affect the risk for coronary events, but it did reduce the risk of invasive breast cancer compared with placebo (hazard ratio, 0.56; 95% CI, 0.38 to 0.83). The rates for total deaths and strokes were no different between groups, but the risk of fatal stroke was greater in raloxifene- vs. placebo-treated women (hazard ratio, 1.49; 95% CI, 1.00 to 2.24). Raloxifene, at present, is approved for the prevention and treatment of postmenopausal osteoporosis. Data from the above-described trials give providers a more comprehensive safety and risk reduction profile for this SERM that will be useful when considering the options for preserving BMD and reducing fractures as well as other health risks in their postmenopausal patients.

**Anabolic and combination therapies**

**Teriparatide and alendronate.** As important as it is to develop new therapies and identify novel drug targets to stave off bone loss, it is equally important to maximize the use of approved therapies—in combination or in sequence—especially if these therapies have different mechanisms of action. For this reason, there is inherent appeal to combining a powerful anabolic agent such as PTH—either the 1–84 or 1–34 form of the hormone—with an antiresorptive agent such as alendronate. The results of this strategy were reported in two studies in 2003—one in women (34) and the other in men (34) with osteoporosis. Adding alendronate to therapy with PTH, in both men and women, blunted the anabolic effects of PTH—both in terms of BMD and bone formation marker responses (34–36). Results from the second year of the PaTH (Parathyroid Hormone and Alendronate) study in postmenopausal women showed that gains in BMD due to 1 yr of PTH therapy were lost if PTH was followed by...
of vitamin D supplements needed to reach them to maintain adequate calcium absorption and bone health. Interestingly, the six experts surveyed varied as to the following: what levels of 25 OH D constituted sufficiency (70 to 80 nmol/liter or 28 to 32 ng/ml); what levels of 25 OH D were optimal to prevent fractures (50 to 80 nmol/liter; 20 to 32 ng/ml); and how much vitamin D3 supplements were needed daily to maintain these levels (800 to 1000 IU vitamin D3). Although the preferred supplement is vitamin D3 and not D2, in the United States high-potency vitamin D3 or cholecalciferol supplements are not available.

How successful are clinicians at maintaining sufficient 25 OH D levels in patients with osteoporosis? In a survey by Holick et al. (41), approximately 50% of 1536 women (average age, 71 yr) from 61 sites across North America had levels of 25 OH D less than 30 ng/ml. All of the patients recruited to this study were being treated with prescription medications for osteoporosis (alendronate, risedronate, etidronate, calcitonin, raloxifene, or teriparatide) but were insufficient in vitamin D. Approximately 60% of the sample was taking at least 400 IU vitamin D daily. Thus, physicians caring for patients with postmenopausal osteoporosis need to devote more effort to achieving vitamin D sufficiency and supplementing their patients with higher doses of the vitamin.

The ability of vitamin D supplements to prevent fractures continues to be discussed. This issue was carefully addressed in a meta-analysis published in 2005. Bischoff-Ferrari et al. (42) found that, in trials that supplemented with 700–800 IU of vitamin D, there was a reduction of hip fractures (by 26%; RR, 0.74; 95% CI, 0.61–0.88) and of any nonvertebral fractures (by 23%; RR, 0.77; 95% CI, 0.68–0.87).

In contrast, a trial done as part of the Women’s Health Initiative reported that the supplementation of postmenopausal women (ages, 50–79; n = 36,282) for 7 yr with vitamin D3 (400 IU) and calcium carbonate (1000 mg) vs. placebo failed to prevent hip fractures (43). There was a slight improvement in hip BMD but an increase in kidney stones. Several issues have been raised regarding this study, including lower rates of adherence to therapy, higher calcium intake at baseline in study participants, and perhaps the selection of a suboptimal vitamin D3 supplement.

Disorders of Parathyroid Function

Calcimimetics act as allosteric modulators of calcium receptors (CaRs) by binding to these receptors on parathyroid cells and mimicking the action of high extracellular Ca2+ to inhibit PTH secretion. The efficacy of the calcimimetic cinacalcet in uremic secondary hyperparathyroidism has been confirmed in an analysis by Moe et al. (9) of several clinical trials that enrolled nearly 1200 hemodialysis patients. These investigators reported that once-daily doses of cinacalcet (30–180 mg) vs. placebo for 6 months lowered serum intact PTH by 56% vs. (10% in controls). Serum phosphorus and Ca2+ levels both fell modestly, whereas the Ca2+ × phosphorus product reached less than 55—the target level recommended by the National Kidney Foundation guidelines—in 65% of cinacalcet-treated vs. in only 36% of placebo-treated controls. This agent is approved by the FDA to treat secondary hyperparathyroidism in patients on dialysis. Ef-
Phosphate Metabolism, Calcification, and Osteomalacia

Bone is the storage site for most of the body’s phosphorus. Mounting evidence indicates that osteocytes—embedded in bone matrix but in close communication with each other, surface osteoblasts, and lining cells via the canalicular network—are the sites for production of several proteins essential to the regulation of phosphate metabolism. The availability of phosphorus has been clearly demonstrated to be a key factor in the orderly regulation of many steps in bone mineralization.

One critical phosphate-regulating factor secreted by osteocytes is FGF-23. This factor acts on the kidney to promote phosphate excretion and reduce 1,25 D production. The evidence implicating FGF-23 in mineral metabolism in health and disease states is impressive (1). FGF-23 plays a causative role in the majority of cases of oncogenic or tumor-induced osteomalacia (44). FGF-23, overproduced by the unusual tumors that cause the syndrome, circulates as an endocrine factor inducing phosphate-wasting, bone demineralization (osteomalacia), and often painful fractures (2). FGF-23 levels tend to be elevated in X-linked hypophosphatemic rickets.

This entity is due to loss-of-function mutations in the coding or regulatory regions of a gene encoding a peptidase on the X chromosome that is thought to participate in some way, likely indirectly, in FGF-23 breakdown and inactivation (3). Point mutations in the protease cleavage site of FGF-23, involving key arginine residues, have been further shown to explain many, but not all, cases of autosomal dominant hypophosphatemic rickets. These have been considered gain-of-function mutations as they reduce the clearance of FGF-23 (4). Autosomal recessive inactivating mutations in GALNT3, an enzyme involved in the O-linked glycosylation of FGF-23 that renders the molecule fully active (15), and inactivating mutations in FGF-23 both cause familial tumoral calcinosis (16). This condition is characterized by hyperphosphatemia with inappropriately normal or elevated 1,25 D levels and ectopic and vascular calcifications. These and many other reports, along with detailed data from several key knockout mouse models, firmly establish the primacy of FGF-23 in the control of normal and pathological calcification and phosphate balance.

Most recently, the noncollagenous bone matrix protein DMP-1 has been shown to participate in the FGF-23-mediated regulation of phosphate metabolism (17, 18, 45). DMP-1, mainly a product of osteocytes, induces them to secrete FGF-23. DMP-1 in the matrix gets phosphorylated. In this form, it promotes skeletal mineralization by osteoblastic cells along with a host of other factors. An autosomal recessive form of hypophosphatemic rickets was just reported to be due to loss-of-function mutations in the DMP-1 gene (17, 18). Abnormal mineralization, rickets or osteomalacia, elevated levels of FGF-23, and hypophosphatemia are the features of this rare disorder. Along with information on the pathogenesis of this form of rickets/osteomalacia came the report of a DMP-1 null mouse model (17). Studies in these mice indicate that DMP-1 may also play a role in mediating the progression of osteoblasts to osteocytes as well as in promoting the synthesis of FGF-23. As Schiavi (45) points out, it has long been held that the kidney controls bone metabolism through PTH and vitamin D, this dogma is now challenged because key products from bone cells (FGF-23 and others) are critical for phosphate handling by the kidney.

Acknowledgments

This paper is dedicated to the memory of Paul Shoback (1917–2006).

Received January 8, 2007. Accepted January 17, 2007.

Address all correspondence and requests for reprints to: Dolores Shoback, 111N, Endocrine Research Unit, 4150 Clement Street, San Francisco, California 94121. E-mail: Dolores.Shoback@ucsf.edu.

D.S. receives research support from the Department of Veterans Affairs Merit Review.

Disclosures: D.S. is a member of the Speakers’ Bureau for Merck and the Advisory Board for Lilly and Company and is a consultant for Merck and Amgen.

References
