CLINICAL OBSTETRICS AND GYNECOLOGY
Volume 56, Number 4, 730–738

Osteoporosis: What's New and on the Horizon

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Abstract: In this review, we consider new concepts in the assessment of fracture risk and pharmacologic therapy for osteoporosis. We discuss trabecular bone score, a new imaging technology that adds information that cannot be obtained by only measuring bone mineral density by dual-energy x-ray absorptiometry. We also discuss innovations in antiresorptive, osteoanabolic, and combination therapy; and newer therapeutic classes, including cathepsin K inhibitors and antisclerostin antibodies. We do not cover agents that have not yet been studied in human clinical trials or that are no longer under active investigation.
Key words: trabecular bone score, denosumab, teriparatide, PTHrP, cathepsin K, antisclerostin

Trabecular Bone Score (TBS)

Bone mineral density (BMD) measurement by dual-energy x-ray absorptiometry (DXA) remains the gold standard for skeletal assessment. However, it does not measure bone microarchitecture, which also contributes to bone strength. To this end, high-resolution peripheral quantitative computed tomography permits the assessment of skeletal microstructure noninvasively. However, high-resolution peripheral quantitative computed tomography is not readily available and is likely to remain a research tool for years to come. The TBS is a novel gray-level textural analysis that uses variograms of lumbar spine DXA images to estimate trabecular microarchitecture. TBS is calculated by applying specific software to DXA images using GE Lunar (Prodigy and iDXA) or Hologic (Delphi, QDR 4500, and Discovery) densitometers. TBS reflects the rate of gray-level amplitude variations in the trabecular bone, which is determined by the skeletal microarchitecture. A high TBS is associated with better trabecular microarchitecture, with more numerous and connected trabeculae, whereas a low TBS indicates worse bone microstructure, that is, low trabecular number and connectivity

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Supported by NIH DK069350, NIH DK32333, and FDA 002525.

J.P.B. is a consultant for Amgen, Eli Lilly, Radius, NPS Pharmaceuticals, Merck, Warner Chilcott, and GSK, and receives research support from NPS Pharmaceuticals and Amgen. The remaining authors declare that they have nothing to disclose.

with high trabecular separation.[1] TBS is highly correlated with measures of bone microarchitecture and biomechanical properties using cadaveric bone as well as in vivo studies.[1–3] More importantly, TBS is associated with fragility fractures in postmenopausal women, independent of BMD measurements by DXA.[4–6] In prospective studies, TBS has been shown to predict osteoporotic fracture risk.[7,8]

Several case-control studies have analyzed the association between TBS and fragility fracture in postmenopausal women.[4,5] In each of these studies, which enrolled approximately 200 women, TBS distinguished between those with and without fracture, with odds ratios (OR) ranging from 2.66 to 3.20 for vertebral fracture.[4,5] Moreover, an OR of 1.95 per SD decline in TBS was found when all types of osteoporotic fractures were considered ($P < 0.001$).[4] Spine TBS was found to be associated with hip fracture in a cross-sectional study of 191 women 50 years of age and older.[6] The odds of presenting with a femoral neck fracture were significantly higher for women with low lumbar spine BMD (OR = 2.2) and low spine TBS (OR = 2.0), even after adjusting for age. The combination of BMD and TBS in the model demonstrated an OR of 2.3 for femoral neck fracture. In addition to predicting fracture risk in postmenopausal women with primary osteoporosis, TBS has also been shown to be associated with fragility fracture in individuals with secondary causes of osteoporosis, including diabetes mellitus, rheumatoid arthritis, and primary hyperparathyroidism.

Prospective studies have confirmed that TBS predicts fracture risk in postmenopausal women and that it can be used as an adjunct to BMD for fracture-risk assessment.[7,8] The Manitoba study[8] enrolled 29,407 women aged 50 years or older, 1668 (5.7%) of whom developed an osteoporotic fracture over a mean follow-up of 4.7 years. Spine TBS and spine BMD predicted fractures equally well. Each SD decline in TBS conferred a 35% increase in the age-adjusted hazard risk for any major osteoporotic fracture, compared with a 47% and 67% increase for each SD decline in lumbar spine BMD or total hip BMD, respectively. Fracture prediction was significantly improved when any BMD measurement (lumbar spine, femoral neck, or total hip) was used in combination with lumbar spine TBS as compared with BMD or TBS alone ($P < 0.0001$). Recent studies have investigated the effect of osteoporosis treatment on spine TBS,[9,10] indicating that bone microarchitecture assessed by TBS is either increased or preserved with antiresorptive therapy.

TBS has the major clinical advantage of being readily available from images obtained through DXA, a test routinely performed to assess fracture risk. Now that the United States Food and Drug Administration has approved TBS technology, it is likely to be applied more widely as an adjunct to standard DXA measurement. Given that TBS demonstrates significant correlations with microstructural indices and has been confirmed as an independent quantitative measure of fracture risk in postmenopausal women and secondary osteoporosis related to several diseases, TBS has clinical utility as an adjunct to BMD for fracture-risk assessment. This additional information may assist in therapeutic decision making.

Antiresorptive Therapy

The human skeleton is constantly being remodeled through a dynamic process of 2 normally balanced phases of bone formation and resorption. Bone formation, carried out by osteoblasts, and bone resorption, implemented by osteoclasts, can be clinically assessed by the measurement of circulating bone formation or resorption markers. Together, these markers are generally called bone turnover markers.

When these 2 processes are balanced, bone is neither gained nor lost. Bone loss arises when bone resorption predominates over bone formation, either because osteoclasts are too active, or because osteoblasts are not active enough. Two classes of drugs for the treatment of osteoporosis are currently available: the antiresorptive and osteoanabolic agents. Although both classes tend to influence bone turnover, they do so in completely different directions. Antiresorptive agents reduce bone turnover, whereas osteoanabolic agents increase bone formation.

As further discussed in this issue by Pinkerton and Dalkin, a new antiresorptive therapy belonging to a new mechanistic class was approved in 2010. Receptor activator of nuclear factor-kB ligand (RANKL) is a key mediator of osteoclast formation, activity, and survival. Denosumab, a fully human monoclonal antibody, binds with high affinity and specificity to RANKL and reduces osteoclast-mediated bone resorption. Denosumab reduces fractures of the lumbar spine, hip, and other nonvertebral sites. It markedly reduces bone turnover as assessed by iliac crest bone biopsy and measurement of circulating biochemical markers of bone turnover. Denosumab is also associated with a linear increase in BMD.[11] The indications for denosumab are as follows; treatment of postmenopausal women with osteoporosis who are at high risk for fracture; treatment to increase bone mass in men with osteoporosis at high risk for fracture; treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer; and treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. Denosumab has been approved by the European Commission to treat women with osteoporosis at high fracture risk and to treat men receiving hormone ablation therapy for prostate cancer. Because of the expression of RANKL in lymphocytes, there was concern that the inhibition of RANKL could lead to an increase in the risk of infection. However, in clinical trials the rate of serious infections was not higher with denosumab therapy. There was a higher incidence of hospitalization for erysipelas or cellulitis when compared with placebo, although the number of events was low.[12]

Osteoanabolic Therapy

Currently, the only available osteoanabolic therapies for osteoporosis are parathyroid hormone (1-84) [PTH(1-84)] and its fully active, foreshortened variant, PTH(1-34) (teriparatide). Both are administered daily by subcutaneous injection for up to a 2-year course. Initial concern for osteosarcoma raised by rat toxicity studies has not surfaced in patients. The incidence of osteosarcoma in patients treated with PTH(1-84) and teriparatide is not greater than what would be expected in the general population not exposed to these PTH formulations.[13] New formulations and dosing regimens of PTH therapy are being studied, along with new innovations in combination therapy with antiresorptive drugs.

DIFFERENT TIMING AND DELIVERY SYSTEMS OF TERIPARATIDE

Weekly Teriparatide Administration

Weekly teriparatide 200 IU (56.5 μg) was tested in a randomized, double-blind, placebo-controlled trial conducted in Japan.[14] A total of 578 Japanese men and postmenopausal women with low BMD and at least 1 vertebral fracture were randomized to receive either study drug or placebo for 72 weeks. Lumbar spine, total hip, and femoral neck BMD increased compared with placebo, and there was a reduction in the relative risk (RR) of vertebral fracture by 80% for those treated with the active drug

(14.5% vs. 3.1%; $P < 0.01$). After completion of the trial, 465 subjects were enrolled in a follow-up study in which patients were treated for 1 year with bisphosphonates, other therapeutic regimens, or no further pharmacologic therapy at the discretion of their physicians.[15] New vertebral fracture occurred in 3.4% of subjects in the postteriparatide group and 13.7% in the postplacebo group (RR = 0.23; 95% CI, 0.10-0.52, $P < 0.05$). Outcomes from the original weekly teriparatide trial are comparable with those obtained with daily teriparatide, with the exception that daily teriparatide decreased cortical BMD of the femoral neck. Weekly teriparatide has been approved in Japan.

Transdermal Teriparatide

Early trials of a transdermal teriparatide delivery system established PTH(1-34) delivery with a rapid time to maximal concentration, comparable area under the curve, and shorter half-life than with subcutaneous administration. A phase II trial randomized 165 postmenopausal women to receive daily teriparatide by a transdermal microneedle patch at doses of 20-, 30-, and 40 μg; 20 μg subcutaneously; or placebo for 6 months.[16] Bone turnover markers increased in all treatment groups in a dose-dependent manner compared with placebo. By 6 months, the teriparatide patch groups led to a dose-dependent increase in lumbar spine BMD, with the highest increase noted in the 40 μg group (+ 5%) compared with + 3.6% in the subcutaneous injection group and −0.3% in the placebo arm ($P < 0.001$ for both comparisons). Total hip BMD was also increased with the 40 μg teriparatide patch arm compared with the subcutaneous and placebo groups ($P < 0.05$).

Delivery of Teriparatide by Chip Technology

A wirelessly controlled microchip containing discrete doses of lyophilized teriparatide was tested over 4 months in 8 postmenopausal women with osteoporosis.[17] The device was implanted in the subcutaneous tissue of the abdomen and a computer-based program communicated wirelessly with the implant to adjust dosing. Escalating doses of subcutaneous teriparatide were subsequently administered to patients for comparison. Teriparatide administration by the implantable microchip increased bone formation and demonstrated pharmacokinetics that were similar to standard daily subcutaneous injections. There were no toxic or adverse events due to the device or to the drug, and patients stated that the device did not compromise quality of life.

PTH-RELATED PEPTIDES [PTHrP(1-36); PTHrP ANALOGUE]

Although PTHrP was first brought to medical attention as the cause of humoral hypercalcemia of malignancy, it has been subsequently demonstrated to have key physiological actions in the skeleton as well as other systems. Similar to PTH in primary hyperparathyroidism, PTHrP is catabolic to bone when administered continuously, and therefore intermittent administration has been studied. Phase I studies showed that PTHrP(1-36) tended to favor a rather exclusive stimulation of bone formation.[18] A phase II trial randomized 105 postmenopausal women to receive daily subcutaneous treatment with PTHrP(1-36) 400 or 600 μg versus PTH(1-34) 20 μg daily for 3 months.[19] Both PTH(1-34) and PTHrP(1-36) stimulated bone formation early, although by study conclusion PTH(1-34) had increased bone formation markers 2- to 4-fold greater than PTH(1-36) at the 600 or 400 μg doses, respectively ($P < 0.05$). As expected, the increase in bone resorption occurred later but the change was not as robust. The increase in bone resorption at 3 months was 3-fold greater for the PTH(1-34) arm than either of the

PTH(1-36) groups ($P < 0.05$), which were not different from each other. At the lumbar spine, PTH(1-34) and PTHrP (1-36) at both doses significantly increased BMD by about 2%. There were small but significant increases in hip BMD in the PTHrP(1-36) group but not in the PTH(1-34) group, and there were no significant differences in BMD at the forearm. There were more frequent episodes of mild hypercalcemia in the PTHrP(1-36) groups as compared with the PTH(1-34) group, but no other differences in adverse events.

An analogue of PTHrP (BA058) has been designed to optimize the osteoanabolic potential of PTHrP. It contains the primary sequence of PTHrP up to residue 22 and differs thereafter by strategically placed amino acid substitutions. BA058 was tested in a phase II multicenter, double-blind, placebo-controlled trial that enrolled 221 postmenopausal women with osteoporosis. Patients were randomized to receive subcutaneous BA058 20, 40, or 80 μg, placebo, or teriparatide 20 μg for 24 weeks.[20] At study completion, 184 patients enrolled in a 24-week extension trial. BMD increased in a dose-dependent manner for BA058 with the greatest efficacy for the 80 μg dose. At 24 weeks, lumbar spine BMD increased 6.7% for the BA058 80 μg arm compared with 5.5% with teriparatide and 1.6% for placebo ($P < 0.001$ for the comparisons to placebo and to teriparatide). Further, increases in lumbar spine BMD were noted during the extension, with a mean percent change at 48 weeks of 12.9% with BA058 80 μg, 8.6% with teriparatide, and 0.7% with placebo. At 24 weeks, significant changes were noted in serum and urine markers from baseline for BA058 40 and 80 μg and for teriparatide. Overall, BA058 was well tolerated with an adverse event profile comparable with the placebo arm. An international phase III placebo-controlled, 18-month study in postmenopausal women is being conducted at this time evaluating BA058 at the 80 μg dose with the primary endpoint of incidence of new vertebral fractures. The trial includes an unblinded positive control arm using teriparatide. In addition, administration of BA058 through a transdermal microneedle technology is also under development and in phase I and II trials (http://www.radiuspharm.com).

COMBINATION OSTEOANABOLIC AND ANTIRESORPTIVE THERAPY

Because of their differing mechanisms of action, the combined use of antiresorptive and osteoanabolic therapy presents, in theory, the opportunity to reduce bone resorption while increasing bone formation. This potential effect of combination therapy could conceivably achieve better results than monotherapy with either agent alone. However, in 2 trials investigating the combination of PTH and alendronate,[21,22] bone markers followed the course of alendronate, not PTH, with reductions in bone markers of formation and resorption. PTH monotherapy was shown to result in greater BMD gains than with combination therapy or alendronate alone, perhaps because of the dominating effects of alendronate on bone-remodeling dynamics when the drugs are used in combination.

Results of these combination therapy studies with alendronate led to the concept that use of an antiresorptive agent that acts on bone resorption but that does not impair the anabolic actions of PTH to increase bone formation may be a more effective approach to combination therapy. To this end, encouraging results were observed with raloxifene and, more recently, with risedronate, both less potent antiresorptive agents than alendronate. The results of these proof-of-concept studies supported the idea that combination therapy might be advantageous but that further investigation would be needed.[23,24] Single dose of zoledronic acid has been studied in combination with

daily teriparatide.[25] A 6-month advantage was seen but by the end of the study, at 12 months, between-group variations were not different from either teriparatide alone (lumbar spine) or zoledronic acid alone (hip). However, if the lumbar spine and hip sites were considered together as a composite endpoint, only combination therapy provided improvements in BMD that were greater than either zoledronic acid or teriparatide alone.

Combination therapy with teriparatide has also recently been studied with denosumab. As a RANKL inhibitor, denosumab blocks a major catabolic pathway for PTH that requires RANKL. With exogenously administered PTH, therefore, denosumab may shift PTH's metabolic venue from a catabolic RANKL-dependent one to the osteoanabolic Wnt signaling pathway.[26] This thinking led to the hypothesis that denosumab and teriparatide in combination may be more beneficial than the combination of teriparatide with other antiresorptives. The Denosumab and Teriparatide Administration Study demonstrated that this combination therapy is beneficial.[27] At 12 months, lumbar spine BMD increased more in the denosumab and teriparatide combination group (+ 9.1%) than the teriparatide alone (+ 6.2%, $P = 0.014$) or denosumab alone (+ 5.5%, $P = 0.0005$) arms. Femoral neck and total hip BMD also increased to a greater extent in the combination group than either monotherapy arm. BMD at the distal radius increased about 2% in the combination therapy and denosumab alone arms, while it decreased in the teriparatide alone group. With combination therapy, bone resorption markers decreased to a similar extent as the denosumab alone arm; however, bone formation markers fell more gradually and to a lesser extent.

It is important to note that these combination studies have not been designed with fracture outcome as an endpoint, and have also been shorter than typical definitive fracture trials. These data should therefore be interpreted with caution.

Newer Therapies

CATHEPSIN K INHIBITORS

Cathepsin K is a protease expressed by activated osteoclasts that promotes degradation of type I collagen. It plays an important role in the process of bone resorption by helping to create the bone-remodeling unit. Several oral compounds have been designed to inhibit cathepsin K in a reversible manner and are now under investigation for the treatment of osteoporosis. Early preclinical and clinical studies have shown that cathepsin K inhibitors reduce bone resorption without suppressing bone formation rate to an appreciable degree.[28,29]

Among the cathepsin K inhibitors studied, ONO-5334 and odanacatib have shown encouraging results in clinical trials. A phase II randomized, parallel group dose-escalation trial evaluated the efficacy, safety, and tolerability of daily ONO-5334 compared with alendronate 70 mg weekly and placebo in 285 Japanese postmenopausal women with osteoporosis.[28] Although the effects of ONO-5334 on bone resorption markers were similar to alendronate, it had a much smaller effect on bone formation markers. Patients taking the study drug had dose-dependent improvements in BMD, similar to alendronate at the 300 mg dose. ONO-5334 was well tolerated, overall, with serious adverse events reported in 11.1% of patients on study drug compared with a 7% incidence in the placebo and alendronate groups. Hypertension and dyspepsia were the most common adverse events reported in the ONO-5334 group.

Similar to ONO-5334, odanacatib (MK-0822) inhibits bone formation markers to a much smaller extent than bone resorption

indices. A randomized, multicenter, placebo-controlled dose-escalation trial enrolled 399 postmenopausal women with low BMD.[29] At 12 months, lumbar spine and femoral BMD increased in a dose-dependent manner, except at the lowest 3 mg odanacatib dose, with further BMD increments noted at 24 months. Bone turnover markers were reduced in a dose-dependent manner, and remained below baseline levels at months 12 and 24. Although bone formation markers initially declined, they gradually increased after 6 months to levels similar to placebo-treated subjects, except at the highest 50 mg dose, in which bone formation markers remained lower than controls throughout the 2-year study. A 1-year extension included a subset of patients who were rerandomized to odanacatib 50 mg weekly or placebo in a double-blind manner.[30] Further gains in BMD were noted from year 2 to 3 in the women continuously treated with odanacatib with a cumulative BMD gain of 7.9% at the lumbar spine, 5.8% at the total hip, and 5.0% at the femoral neck. In the subjects allocated to placebo after 2 years of active drug, there was significant bone loss, particularly during the first 6 months after the study drug was discontinued. After 12 months without further treatment, femoral neck BMD still remained slightly increased (+ 2.3%) over baseline; however, BMD at the lumbar spine, total hip, and trochanter returned to baseline levels. A rapid increase in bone resorption markers was seen after odanacatib was discontinued, and levels remained above baseline after 12 months. Bone formation markers increased during the first 6 months off therapy, followed by a return to baseline levels. The rapid reversibility observed upon discontinuation of odanacatib is similar to that seen with most other antiresorptive agents, such as estrogens, selective estrogen receptor modulators, and denosumab.[11] Odanacatib was well tolerated with reports of adverse events that were similar to placebo with the exception of a greater number of noncomplicated urinary tract infections in the odanacatib group (12 vs. 3).

In a 2-year phase III trial, 214 postmenopausal women with low BMD were randomized to receive weekly oral odanacatib 50 mg or placebo.[31] The odanacatib arm showed significantly greater gains in BMD at the lumbar spine, femoral neck, total hip, and trochanter as early as 1 year of treatment, and treatment differences at 2 years were 5.4%, 3.8%, 3.3%, and 5.5%, respectively. Odanacatib also increased finite element-estimated strength at both the hip and spine. Other phase III trials are currently ongoing.

SCLEROSTIN

Wnt/β-catenin signaling promotes bone formation. Sclerostin is a negative regulator of this pathway and has thus provided a possible target for therapeutic intervention.[32] Romosozumab (AMG-785, Amgen) is the first human sclerostin antibody to be studied.[33] A phase I trial of romosozumab showed, in a dose-dependent manner, increments in bone formation markers and reductions in bone resorption markers.[33] Three months of exposure to drug led to increases in lumbar spine and total hip BMD at virtually all doses. A phase II trial compared different subcutaneous regimens of romosozumab (monthly: 70 mg, 140 mg, 210 mg; every 3 mo: 140 mg, 210 mg) to placebo, teriparatide 20 mg subcutaneously daily, and oral alendronate 70 mg once weekly.[34] After 1 week of treatment, bone formation markers increased and bone resorption markers decreased compared with baseline. By 12 months, BMD at the lumbar spine, total hip, and femoral neck increased with all regimens of romosozumab as compared with placebo ($P < 0.005$), with the greatest densitometric gains in subjects taking the 210 mg monthly dose (11.3% at lumbar spine and 4.1% at total hip). BMD increments were significantly less with alendronate and teriparatide than with romosozumab ($P < 0.0001$). Mild reactions at

injection sites were higher with romosozumab (12%) versus placebo (4%), but overall, adverse events were balanced between romosozumab groups and placebo. Further studies are ongoing.

Blosozumab is another antisclerostin antibody under development.[35] A randomized, parallel-design, double-blind placebo-controlled trial investigated the effects of different doses of blosozumab in 154 postmenopausal women with low BMD. Four subcutaneous regimens (270 mg every 12 wk; 180 mg every 4 wk; 180 mg every 2 wk; and 210 mg every 2 wk) were compared with placebo over a 12-month period. The primary endpoint was the densitometric response at the lumbar spine. The percent change in lumbar spine BMD from baseline for the 4 blosozumab doses were + 6.7%, + 8.4%, + 14.9%, and + 17.8%, respectively, versus − 1.5% for placebo. Subjects treated with blosozumab experienced mild to moderate injection-site reactions, although other adverse events did not differ across treatment groups.

Summary

In this review, we have discussed TBS, a new clinically available tool to aid in the assessment of fracture risk. We have reviewed new developments in the therapeutics of osteoporosis with established antiresorptive and osteoanabolic categories of pharmacologic osteoporosis therapy, as well as new classes that are under active investigation: cathepsin K inhibitors and sclerostin antibodies. These newer developments hold promise for further advances in the diagnosis and management of osteoporosis.

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