A rational approach to evidence gaps in the management of osteoporosis

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ABSTRACT Major advancements in the treatment of osteoporosis have occurred over the last decade. Therapies including the anti-resorptive drugs such as alendronate and risedronate have been shown in randomized placebo-controlled trials to increase bone mineral density and reduce fracture risk. Anabolic therapy in the form of parathyroid hormone has been introduced as the first treatment to build bone mass. However, gaps in our knowledge about specific management issues that arise frequently among primary care providers persist. In this paper, three common clinical scenarios are discussed: a postmenopausal woman with only slightly reduced bone mineral density; an osteoporotic woman on anti-resorptive therapy for more than 5 years; and a woman who continues to fracture despite treatment. Evidence gaps in each treatment scenario are presented, and rational approaches to management are suggested.

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The care of patients with osteoporosis has advanced considerably in the past decade largely due to publication of several large randomized placebo-controlled trials for agents such as parathyroid hormone, the bisphosphonates, raloxifene, and estrogen. However, evidence gaps persist, and these can cause difficulty in clinical decision-making. In this review three scenarios, in which appropriate therapeutic choices are not supported by robust evidence, are presented to illustrate the dilemmas currently facing clinicians. These include: the appropriate management of postmenopausal women with only modest reductions in bone mineral density; the duration of antiresorptive therapy in women with osteoporosis; and the role of combination therapy, if any, in the management of patients who continue to fracture.

Clinical scenario 1

A 55-year-old recently postmenopausal white woman with no personal history of fracture has osteopenia, with a bone mineral density at the lumbar spine of 1.5 SD below that of young, ethnicity-matched values (ie, T-score = −1.5).

Osteoporosis is defined as a condition of skeletal fragility characterized by reduced bone mass and microarchitectural deterioration predisposing a person to an increased risk of fracture.\(^1\) On the basis of many studies it is now clear that a low bone mineral density is a very strong predictor of future fracture,\(^2\) and that risk increases with age for any given T-score.\(^2\) But the risk of fracture over the next 5 years for a 70-year-old woman is greater than that of a 50-year-old woman even with the same T-score, supporting the thesis that age is an independent and strong risk factor for osteoporotic fractures. To date, there is little evidence of any health consequences from low Bone mineral density, other than the potential risk of fracture. Therefore the focus of a management strategy should center on preventing future fractures in this woman.
However, comparatively little data regarding the magnitude of the association of low bone mineral density and fracture risk in younger postmenopausal women exist. The strongest evidence comes from the National Osteoporosis Risk Assessment (NORA) in which 200,160 postmenopausal U.S. women in primary care practices throughout the country were followed for a 12-month period for self-reported fractures. Approximately 53% of participating women in NORA were between the ages of 50 and 64.

Bone mineral density was measured at one peripheral site (heel, forearm or finger) using one of several technologies (ultrasonography, peripheral dual x-ray absorptiometry [DXA], or single radiograph absorptiometry). In the NORA cohort, there was an increased risk of fracture for T-scores \(< -1\), despite different prevalence estimates for low bone mineral density by device. Although older women (>65 years) sustained the majority of fractures in this cohort, women younger than 65 years of age accounted for one-third of all fractures and one-fifth of the hip fractures. In addition, 31% of this younger cohort had low bone mineral density on these peripheral devices (T-score \(< -1\)).

The incidence of fractures increased as the T-score decreased, similar to data from older women, and the relative risk of fracture was 1.5 for each SD decrease in bone mineral density for both age groups. Thus, the ability to predict risk of fractures in younger postmenopausal women appears similar to fracture risk prediction in older women.

The evidence gap becomes noticeable, however, when trying to assess individual fracture risk using these data. In the NORA study, the absolute fracture risk for younger women was much lower than for older women, despite the predictive ability of the measurement tools. For example, in the younger age group, the overall incidence of osteoporotic fractures over 1 year was one-half that of the older group (8.4, 95% confidence interval [CI] 7.9–9.0 vs 16.5, 95% CI 15.6–17.3 per 1000 person-years, respectively).

Therefore, it is unclear at what point intervention to prevent fractures is necessary, or how cost effective such therapy would be in a woman with a low absolute fracture risk despite a modest reduction in bone mineral density.

In the first clinical scenario, this patient has a bone mineral density labeled “osteopenia” by World Health Organization diagnostic criteria. However, this is not a clinically useful term, nor does it allow for selection of patients at greatest risk, particularly because previous fractures far outweigh low bone mineral density in this age group as a risk factor for subsequent fractures. Should this woman be offered pharmacological therapy? The FDA-approved drugs for the prevention of postmenopausal osteoporosis include: alendronate, risedronate, ibandronate, raloxifene, and estrogen. However, the appropriate decision is less clear-cut because virtually all the prevention trials used hip bone mineral density as primary outcomes rather than fractures. In fact, this patient would not have met the entry criteria for any pivotal antifracture efficacy trial except the Women’s Health Initiative (WHI), which did not select subjects based on bone mineral density or presence of fractures. Notwithstanding these caveats, there are some data to support the use of antiosteoporosis drugs in women with low T-scores to prevent fractures. In the Fracture Intervention Trial (FIT), use of alendronate in women (ages 55 to 80) with femoral neck T-scores of \(-1.6\) to \(-2.5\) decreased the risk of vertebral fracture over a mean 3.8-year period. Fracture reduction was most prominent for women who had a prior vertebral fracture. On the other hand, for women without a vertebral fracture, the absolute benefit was lower and the confidence intervals wider, limiting the strength of this association. The patient in the first clinical scenario does not have a known vertebral fracture and has been labeled “osteopenic” based solely on her bone mineral density, a misleading term for a nondisease entity. In this case, her absolute fracture risk is relatively low.

A common argument for early pharmacologic intervention is the prevention of further bone loss over time in order to prevent an osteoporotic fracture or a very low bone mineral density. Many studies support the effectiveness of therapeutic regimens to increase bone mineral density in recently menopausal women. Alendronate and risedronate are approved for prevention at doses of 35 mg once a week for both therapies. Similarly, estrogen has been shown to prevent bone loss in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial of women with a mean age of 55 years. In that trial, women in the placebo arm lost 1.8% of spine bone mineral density and 1.7% of hip bone mineral density over 3 years. But caution is necessary in interpreting rates of mean bone loss at any given interval for 3 reasons: there is significant heterogeneity among various cohorts of postmenopausal women; regression to the mean is common so that rapid loss one year might be followed by gain the second year; individual patients over a decade of follow-up have variable mean rates of loss.

A reasonable approach to this patient would be to encourage her to supplement her diet with adequate calcium, vitamin D and to increase her weight-bearing exercise. Vitamin D supplementation may improve muscle strength and prevent falls in older individuals. Additional approaches could include use of low or ultra-low dose estrogen, raloxifene or an oral bisphosphonate. Although raloxifene and ibandronate have not yet demonstrated hip fracture prevention, this particular fracture is less prevalent in the early postmenopausal years when radial and vertebral fractures are much more common. Raloxifene use is often limited by an increased incidence of hot flashes and thromboembolic events, whereas the cardiovascular safety profile still needs to be confirmed in primary outcome trials. The effects of long-term oral bisphosphonate therapy are still unclear but are relevant to considering initiation of bisphosphonate therapy in younger postmenopausal individuals.

In summary, there is not enough evidence to recommend a unitary approach for this particular patient. Continued monitoring of bone mineral density by DXA to assess the rate of bone loss in this patient, as well as encouragement of...
Clinical scenario 2

This 70-year-old white woman with a history of osteoporosis by bone mineral density has been on alendronate for the past 8 years. She has suffered no fractures and her spine bone mineral density has increased 8%.

Bisphosphonates have been in widespread clinical use for more than a decade for the therapy of postmenopausal osteoporosis. This is because there is strong evidence for their efficacy in preventing fractures. However, those pivotal trials were typically only 2 to 3 years in duration. Extension studies from those trials have recently been completed and provide some insight into the question of how long an individual should be treated.26,27 A total of 247 postmenopausal women randomized to 5 or 10 mg daily of alendronate participated in the first of 2 follow-up extension trials for a total of 10 years.26 After a decade of use, bone mineral density continued to increase at several sites compared with baseline, although most of the increase occurred during the first 5 years of therapy. In the second study, the FIT Long-Term Extension (FLEX), 1099 women with an average duration of use of 5 years were re-randomized for an additional 5 years to alendronate or placebo.27 The FLEX trial demonstrated that spine bone mineral density increased, whereas hip bone mineral density was stable from year 5 to year 10. A similar finding was noted in a 2-year extension of a large risedronate trial.28 In that study, 136 subjects were followed for an additional 2 years (year 6-7) and all subjects received risedronate. This trial demonstrated a continual increase in spine bone mineral density.29 Taken together, these extension trials suggest that long-term oral bisphosphonate therapy results in either maintenance of bone mineral density or continued increase.

Unfortunately, there are limited data to support the antifracture efficacy of the bisphosphonates beyond the 3-5 years of the extension trials. The first alendronate extension study assessed clinical fractures during the last 5 years of the 10-year follow-up, but rates of fracture could not be calculated accurately because the date of occurrence within the observation interval was unknown.26 In the FLEX trial, clinical spine fracture risk was reduced but morphometric vertebral (ie, diagnosed by radiographs) and nonspine fracture risk were similar between women treated for 10 years and those treated for 5.30 Similarly, although the placebo-controlled extension trial for risedronate reported a decreased risk of new vertebral fracture in years 4-5, there was no statistically significant decrease in nonvertebral fractures.28 Moreover, in years 6-7 of the trial, which was not controlled, there was no change in the rate of new vertebral fractures in the group receiving risedronate for 7 years.29 These data and the FLEX trial findings suggest that fracture rates do not decrease with prolonged bisphosphonate treatment. To establish safety, it is important to examine the effects of long-term bisphosphonates on bone microarchitectural structure. Bisphosphonates exert their antifracture efficacy predominantly by decreasing bone resorption resulting in a consistent decrease in overall bone turnover. This leads to an increase in total mineral content per unit volume of tissue but not an increase in bone mass as widely believed. Normal skeletal repair is dependent on this orderly process of bone turnover characterized by bone resorption followed by bone formation occurring at multiple skeletal sites.

Concerns have been raised as to whether bisphosphonates may result in over-suppression of bone turnover, thereby limiting normal physiologic repair of microfractures or cracks and impairing overall bone strength. The presence of microfractures has been reported with high-dose bisphosphonate administration in some animal models31 but not others,32 and none of these studies have found impaired mechanical strength as a consequence.33 But the question remains: is prolonged suppression of bone turnover by bisphosphonates too much of a good thing?

During long-term administration of alendronate therapy, markers of bone resorption (urinary N-telopeptides) and bone formation (bone-specific alkaline phosphatase) remained suppressed.26 In the last 5 years of FLEX, although N-telopeptide levels rose in women who took only alendronate for the first 5 years, there was still a marked suppression at year 10. Similarly, in the risedronate trials, there was a sustained reduction in markers of bone resorption in those still on active drug (ie, 63% decrease in NTx) at 7 years.29 Despite these findings, at least in the FLEX trial there was absolutely no evidence to suggest that prolonged suppression of bone resorption resulted in a greater risk of fracture even with a decade of use.

Bone histomorphometry obtained in women on alendronate therapy does not demonstrate microarchitectural deterioration after 3 years of therapy (ie, doses between 5 mg and 20 mg daily).34 Bone turnover at trabecular sites was markedly reduced but there was normal mineralization, an important aspect of long-term safety.34 Similarly, histological evidence from paired bone biopsy specimens in 55 postmenopausal women after 3 years of risedronate therapy (5 mg daily) show reduced bone remodeling but do not show any adverse effects on histomorphometric parameters.35,36 This is relevant because a non-nitrogen containing bisphosphonate, etidronate, has been associated with osteomalacia or defective mineralization in some cases.37 In the FLEX trial, 29 women treated for about 5 years and then followed with either placebo (n = 14) or alendronate (n = 15) revealed that qualitative bone parameters were normal.38 Unfortunately, the number of subjects studied by bone biopsy on long-term therapy is quite limited.

Recently, the controversy surrounding long-term bisphosphonate use has taken an interesting turn. A case series reported 9 patients who had delayed healing of fractures after long-term bisphosphonate therapy with markedly...
suppressed bone formation at trabecular bone surfaces on biopsy specimens. These subjects had alendronate for 3-8 years and had incident fractures at 1-8 years of therapy with delayed healing of fracture. Concomitant therapies included glucocorticoids (2 patients) and estrogen (3 patients) treatment. Five of the 9 subjects healed their fractures 3-8 months after cessation of the bisphosphonate, although it is unclear whether it was associated with bisphosphonate use. Adding fuel to the fire, uncontrolled retrospective case studies have recently reported osteonecrosis of the jaw occurring in patients with dental procedures on intravenous bisphosphonate therapy for cancer treatment, and in rare reports of individuals receiving intravenous or oral bisphosphonate therapy for osteoporosis. Osteonecrosis of the jaw was not reported in the 10-year follow-up of alendronate for postmenopausal osteoporosis. Thus, it is unclear whether a causal relationship exists for either delayed fracture healing or osteonecrosis, but these case reports warrant further investigation.

A final consideration in this second scenario relates to post-cessation changes in bone mineral density, bone turnover, and fracture end-points. Two separate trials with alendronate reported that participants who discontinued therapy after 5 years and received placebo for the remaining 5 years had minimal decreases in bone mineral density at the spine and hip. In addition, as noted previously, bone turnover markers increased after cessation but remained well below the pretreatment levels over a 3- to 5-year period. A trial in Danish women given higher doses of alendronate (20 mg/d) for 2 years had continued suppression of bone turnover markers 5 years after cessation relative to their baseline values. These data suggest there is a residual effect of bisphosphonates on maintaining bone mineral density and suppression of bone turnover after cessation of drug therapy. Bisphosphonates appear to be incorporated long-term into the skeleton, primarily at active sites of bone remodeling but potentially at future sites of remodeling as well. This may be the reason for a prolonged effect on bone turnover even after the drugs are stopped. This is in sharp contrast to estrogen therapy that appears to rapidly lose its beneficial effect on bone mineral density after cessation. In fact, some evidence suggests that fracture risk in women who have been off estrogen for 5 years may be the same as never-users of hormone therapy. As noted previously, fracture data are limited and it is unclear whether cessation of a bisphosphonate would result in rapid increases in fracture risk.

These data help define the risks and benefits of continued long-term bisphosphonate therapy but do not provide reassurance of long-term safety or fracture risk reduction. In the absence of strong evidence, it seems prudent that individuals at highest risk for fracture, such as an elderly woman with low bone mineral density or any patient who has a prior osteoporotic fracture, should not be taken off bisphosphonates as long as they are not having recurrent fractures. Individuals who have been on long-term therapy but may not be at high risk of fracture could consider stopping therapy after 5 years given the evidence for a sustained effect on bone mineral density and bone turnover. If this course were chosen, it would be important to obtain follow-up DXA scans within 2 years. In the second clinical scenario, there is no clear answer but a reasonable approach would be to continue bisphosphonate therapy because her age puts her at a higher short-term risk of fracture and she has evidence of bone mineral density response without clinical adverse effects. On the other hand, stopping for 3 to 5 years may be judicial, as long as the patient is aware that she may need to restart treatment in the future, or that other forms of therapy might be considered, particularly if there is bone loss or new fractures.

Clinical scenario 3

A 75-year-old white woman sustained a vertebral fracture while on bisphosphonate therapy for 6 years.

Women can continue to fracture on antiresorptive therapy even though fracture risk reduction is significant with these drugs. Unfortunately, there is little evidence regarding fracture efficacy if therapies are combined. Most combination trials included antiresorptives alone, commonly estrogen ± progesterin or raloxifene, combined with alendronate or risedronate. These trials uniformly demonstrated improvement in bone mineral density with combination therapy, but fracture efficacy was never established. With the advent of anabolic therapy (PTH 1-34) a different question arises, ie, is there synergism between an anabolic and antiresorptive drug? The antiresorptives decrease bone resorption by impairing the action of osteoclasts and consequently also decrease bone formation because the 2 processes are tightly coupled. Anabolic agents target osteoblasts and enhance bone formation while simultaneously increasing bone turnover. Preclinical evidence had suggested there might be an additive effect by combining an antiresorptive with an anabolic agent. However, clinical trials have not borne out that promise.

Parathyroid hormone, when added to established hormone therapy, increased bone mineral density and reduced vertebral fracture incidence when compared with hormone therapy alone in two very small randomized trials. However, in the post-WHI era, fewer women are choosing hormone therapy. Moreover, in light of the WHI data, a trial to prove superiority of combination therapy versus hormone replacement with respect to fracture efficacy would require tens of thousands of subjects in each of the 2 treatment groups. With respect to parathyroid hormone plus alendronate, an early study in 10 postmenopausal women suggested that parathyroid hormone stimulated bone formation even in the presence of alendronate, a potent bisphosphonate. But two recent trials using a concurrent combination of parathyroid hormone with alendronate in postmenopausal women and men showed that the combination was no better.
than monotherapy alone.\textsuperscript{60,61} Moreover, the anabolic effect of parathyroid hormone on vertebral trabecular bone mineral density, particularly by quantitative computed tomography, was blunted when combined with alendronate. Biochemical bone turnover markers also revealed that the concurrent combination therapy group had lower bone formation indices compared with parathyroid hormone alone.

A more relevant clinical question is whether pretreatment with an antiresorptive (vs concurrent therapy) alters bone responsiveness to parathyroid hormone and precludes use of these agents. Animal data in ovariectomized rats suggest that pretreatment with estrogen, raloxifene or alendronate can affect new bone formation with teriparatide (PTH1-34).\textsuperscript{62} In humans, the bone mineral density response to teriparatide may be different when women are pretreated with raloxifene compared to those treated with alendronate. One uncontrolled study administered parathyroid hormone for 18 months to 59 postmenopausal women who had previously received raloxifene or alendronate therapy for 18-36 months. Bone mineral density responses were greater in the pretreatment group with raloxifene (+10.2% spine; +1.8% total hip) than the alendronate group (+4.1% spine; no change total hip).\textsuperscript{63} This difference could be related to the intensity of suppression in bone resorption, although conclusions about these data should be tempered by the observational nature of the study.\textsuperscript{63} More trials are needed to conclusively answer the question of adding parathyroid hormone to women already on a bisphosphonate.

Evidence is emerging, however, that an antiresorptive following therapy with parathyroid hormone will preserve bone gains accrued on parathyroid hormone therapy. An observational study of 66 postmenopausal women treated with 3 doses of recombinant human parathyroid hormone (1-84) for 1 year followed by alendronate for 1 year reported significant bone mineral density gains that were comparable to the first year of parathyroid hormone.\textsuperscript{64} Recent data from the Parathyroid Hormone and Alendronate for Osteoporosis (PaTH) trial supports this premise by showing that 1 year of alendronate following parathyroid hormone led to a significantly greater increase in spine and hip bone mineral density than parathyroid hormone followed by placebo.\textsuperscript{65}

The use of parathyroid hormone as an adjunctive therapy for recurrent fracture is appealing. However, these data highlight the uncertainty regarding the most effective use of this agent in relation to the concurrent or sequential administration of an antiresorptive. Parathyroid hormone has also been used in a cyclical manner as in a few small trials that raise the question of whether less frequent dosing may be as efficacious and potentially more cost-effective.\textsuperscript{66} Parathyroid hormone therapy costs about $7200/year, and the cost-effectiveness of its use in combination with antiresorptive agents has not been established.

In the third scenario, this patient could be a candidate for parathyroid hormone therapy due to recurrent fractures on alendronate therapy. Contraindications to parathyroid hormone include renal insufficiency, renal stones or hyperparathyroidism. Parathyroid hormone treatment is currently limited to 2 years by the US Food and Drug Administration due to concerns about osteosarcoma in studies of rats on high-dose lifelong therapy. If parathyroid hormone therapy is to be initiated, then alendronate should be stopped. It is unclear whether this patient should go directly onto parathyroid hormone or whether she should wait for several months after cessation before starting therapy. After discontinuation of parathyroid hormone, a bisphosphonate will need to be restarted because bone loss can occur if parathyroid hormone is not followed by an antiresorptive.\textsuperscript{65} Alternatively, she could continue on bisphosphonate therapy with close surveillance for additional fractures. Regardless of the therapeutic plan, it is important to emphasize that currently we cannot cure osteoporosis; rather, our best treatment options only reduce fracture risk by 50%.

Conclusions

Clinicians and their patients with osteoporosis can choose from several pharmacological agents with established efficacy for fracture risk reduction. However, some management decisions are not clear-cut or supported by evidence, as noted in these 3 cases. In this review, a rational method for deciding on appropriate therapy for these clinical scenarios is presented. Ultimately, however, evidence from large-scale randomized trials will dictate the optimal approach to these particular situations.

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