

Clinicians' Forum

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members, experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

Participants

Paul D. Miller, MD
Medical Director
Colorado Center for Bone Research
Lakewood, CO

Marcie K. Richardson, MD
Assistant Director of Ob/Gyn for
Clinical Quality
Harvard Vanguard Medical Associates
Boston, MA

J. C. Gallagher, MD
Professor of Medicine
Department of Metabolism
Creighton University
Omaha, NE

Michael R. McClung, MD
Director
Oregon Osteoporosis Center
Portland, OR

Question: How would I counsel a woman in early menopause (under age 45 years) with a T-score of -2.0 and, if prescribing drugs, which would I choose and why?

Answers:

The case described is a common scenario in clinical practice in the United States. More postmenopausal women fall into this clinical profile, in part because of the ramifications of the Women's Health Initiative (WHI) and the subsequent broad recommendations from the FDA as well as many other professional organizations suggesting that hormonal therapy be used only for menopausal symptoms.¹⁻⁴ Assuming this

patient has no menopausal symptoms and consideration for pharmacologic therapy is only to protect her skeletal health, the choices range from no additional intervention beyond vitamin D and calcium supplementation and exercise, to one of the FDA-registered pharmacologic agents for the prevention and/or treatment of postmenopausal low bone mass.

1. She may have never previously lost any bone mineral density (BMD) before this bone mass measurement was obtained, since peak adult bone mass is normally distributed.⁵
2. Her absolute fracture risk for any fracture over 10 years without any intervention is low.
3. Most of the pharmacologic clinical trials that have led to the approval of agents to "treat" postmenopausal low bone mass and also show fracture risk reduction have randomized patients 60 years of age and older. Thus, if any osteoporosis-specific pharmacologic agent is prescribed, it is done with the knowledge that there are no data indicating that one can reduce this younger postmenopausal woman's 1- to 5-year fracture risk, and that initiation of any agent would be for the intent of preventing BMD from declining, with the unproven hope that lifetime fracture risk can be reduced.^{6,7}

There are several other considerations in making a clinical decision with regard to this patient:

1. What are her additional risk factors? Certainly, if she has had a fragility fracture (from age 45 years onward), her fracture risk is high enough to strongly consider pharmacologic therapy, as shown in the 1-year fracture risk data from the National Osteoporosis Risk Assessment (NORA).⁸
2. Without a pre-existing fracture, her fracture risk is greater at a T-score of -2.4 than at a T-score of -1.4, and she

would fall into the National Osteoporosis Foundation's (NOF) guidelines that suggest treatment even without any other risk factors.⁹ Yet, increased age is a very strong risk factor for fracture, even at the same level of BMD, and since she is young, her 10-year risk for hip or all fractures is low.¹⁰ However, it is not zero. As recently shown in the NORA data, 37% of all fractures and 20% of the hip fractures that occurred in the first year of the NORA follow-up occurred in postmenopausal women under the age of 65 years.¹¹ Since none of the NORA women were under the age of 50 years, the data derived from NORA may not be applicable to this postmenopausal woman, whose age is less than 45 years.

After working up this patient for conditions that could have possibly led to prior bone loss (celiac disease, hyperparathyroidism, etc) and, if she had no prior fragility fracture, I would "watch" this patient on vitamin D, calcium and exercise alone. On the other hand, if she had a prior fragility fracture, or lost BMD 2 years later when the BMD is remeasured, then I would intervene beyond vitamin D, calcium and exercise alone. If her spine BMD is low and her hip BMD is normal, then raloxifene would be a good choice, since it does reduce the risk of vertebral fractures. On the other hand, if her hip BMD is low, then one of the bisphosphonates, alendronate or risedronate, would be the optimum choice, since these agents reduce the risk for both vertebral and nonvertebral fractures. How long a younger postmenopausal woman should be treated with bisphosphonates is yet another important area for discussion and dialogue.¹² Neither calcitonin (not



Paul D. Miller, MD

approved for prevention) nor teriparatide (rh 1-34 parathyroid hormone; approved for “high-risk” patients) would be appropriate choices in this patient.¹³

— Paul D. Miller, MD

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Those of us who care for midlife women face this question—or variations on it—frequently. What is the best way to manage relatively young women whose bones are thin and whom we know will be losing more bone in the post-immedi-

ate postmenopausal years? The evidence is limited at best. No one over the age of 70 even had a bone density measurement in their 40s, much less an intervention to prevent osteoporosis and fracture.

So, in the absence of a clear right answer, what data can we bring to the table to guide the conversation about what is best for our patient? First the question of secondary causes of bone loss should be considered and ruled out. Our patient will lose bone over the next 6 years, as she is menopausal—probably at the rate of about 2% per year. On this trajectory, she will be osteoporotic at a relatively young age.

That is the bad news. The good news is that at her current age her risk for fracture is not substantially higher than that of women with much better bone. So the dilemma we face is should we, as the NOF recommends, treat this woman with pharmacologic agents to prevent bone loss and, hopefully, fracture in the coming decades—even though the efficacy of this approach is not proven any more than the ability of estrogen to prevent heart disease was proven in the 1990s?



Marcie K. Richardson, MD

The non-interventionist approach, which would include weight-bearing exercise, calcium and vitamin D supplementation with close follow-up, can be justified by the patient’s low fracture risk today. Maybe our patient won’t lose bone as fast as most postmenopausal women her age.

We will know more about the long-term effects of the relatively new bisphosphonates, and risk-benefit data continue to come in about estrogen. There will be new, potentially better drugs. There is much to be said for waiting to use drugs.

Additional risk factors, as well as patient preference, might drive a discussion of therapy now. For instance, if

this patient has a mother with severe osteoporosis, she may not be willing to delay treatment. Today, the choices are limited to bisphosphonates (alendronate and risedronate) or estrogen. Why not raloxifene? Well, it has the thrombotic risk of estrogen and has not been shown to prevent the most devastating osteoporotic fracture—the hip.

Now which? In fact, a strong case could be made for estrogen. The doses of estrogen that have been shown to be bone trophic are much lower than those this woman would have been exposed to if she were premenopausal, as most of her age-matched sisters are. The WHI gave us strong evidence that estrogen reduces fracture in women who were not chosen because of their fracture risk—in contrast to the studies used to get FDA approval for the bisphosphonates, in which the patients were generally elderly with osteoporosis. Estrogen’s appeal would be increased if our patient had menopausal symptoms.

If our patient is afraid of the risks of estrogen, bisphosphonates are an alternative. Choosing the particular estrogen or bisphosphonate would depend on several factors—not the least of which is the patient’s drug plan. In keeping with current standards, the estrogen dose should be low.

Advising our patient is not simple, and requires much extrapolation of the evidence. There is room for personal preference. And the decision can be reconsidered as data accumulate or the patient’s circumstances change.

— Marcie K. Richardson, MD

The presence of risk factors, particularly low body weight (< 127 lbs) and a history of previous fracture, lowers the threshold for intervention to a T-score less than -1.5.

There are no systematic studies of any bone-active agent on bone loss in

women with an early menopause; this group may need larger doses.

Estrogen. Because a woman with an early menopause suffers from estrogen deficiency, the physician also has to consider the potential for developing premature heart disease. There are also symptomatic problems of vaginal dryness and vasomotor symptoms. If the patient has menopausal symptoms, then estrogen should be the number-one choice. It is highly effective at preventing bone loss and fractures, and the WHI suggests that it may be the most effective agent for preventing fractures in women with low bone mass/osteopenia. Recent data show that lower doses of estrogen (eg, conjugated equine estrogens 0.45 mg and 0.30 mg, transdermal estradiol 0.025 µg) prevent bone loss in women in their mid-fifties. The type of hormones used (estrogen only or estrogen/progestin) may depend on whether early menopause is surgically induced or natural. Treatment should be continued for at least 10 years. The WHI showed that the risk for cardiovascular events, stroke and breast cancer are not increased in women within 10 years of menopause who receive estrogen only (conjugated equine estrogens, 0.625 mg). For women who received estrogen and progestin, there was no significant risk in the first 10 years for cardiovascular events and strokes; however, there was a small increase in breast cancer.

Bisphosphonates (*alendronate, risedronate, ibandronate*). These agents would be the first choice for women who cannot take estrogen for medical reasons (eg, history of breast cancer, venous thrombosis).

There are no data on the dose needed to prevent bone loss in women with an early menopause; most studies have been carried out in women in their sixties. All of these agents prevent bone loss, and there are emerging data that this group may prevent fractures in

women with low bone mass. Much of the data are derived from retrospective post hoc analysis. However, bone loss is more rapid in the first 5 years postmenopause, and more data on bisphosphonates in this group are needed. There do not seem to be any increased problems after 10 years of alendronate use; however, assessment of safety is not as comprehensive as for estrogens. Any ongoing history of gastric symptoms would count against their use, however new monthly, rather than weekly, regimens may overcome the gastric problem.

SERMs. Raloxifene was the first of this group of compounds to be tested in postmenopausal women. There are no studies in an early menopause group, but raloxifene prevents bone loss in women in their early fifties. Its potency on bone is almost equal to that of lower estrogen doses, and retrospective analysis shows less fractures in women with low bone mass. It does reduce breast cancer and cardiac events in those at highest risk. Raloxifene is the logical choice for women who are fearful of breast cancer or who have a high cardiovascular risk profile. It does carry about the same risk of venous thrombosis as do estrogens.

Calcium supplements. As a primary preventive therapy, calcium is not effective in preventing early postmenopausal bone loss. Its main value is as adjunctive therapy combined with the above bone-protective agents. The general recommendation is for 1,500 mg/day, and it should be combined with vitamin D (400 IU) in the winter months.

Anabolic agents. There is no indication for using anabolic agents such as parathyroid hormone in the treatment of low bone mass.

—J. C. Gallagher, MD



J. C. Gallagher, MD



Michael R. McClung, MD

This patient who has experienced early menopause has a BMD value that is appropriately described as being at the lower part of the normal range for young women. She has not necessarily experienced bone loss. In the absence of medical problems that cause bone loss (eg, steroid use), it is probable that this BMD value reflects her peak bone mass.¹ Bone loss does not occur in healthy premenopausal women until just prior to menopause.² However, it would be important to exclude (on the basis of history and laboratory tests) underlying medical or metabolic causes of low bone density before prescribing a potent bone-active drug.

Osteomalacia, osteogenesis imperfecta and other bone diseases can present as low BMD and are treated very differently than osteoporosis.

If the patient is otherwise healthy, she will be expected to lose 6-10% (0.5-1 T-score) of her bone mass in the spine over the next 5 years.² The rate of bone loss will then slow considerably. Loss of bone mass in early menopause can, in some cases, be associated with significant deterioration in the architecture and structure of trabecular bone.³ Although her risk of having a fracture in the next 5 years is low, she is a candidate for therapy to protect her from the bone loss that will occur during that time. General measures such as adequate calcium intake and exercise are important, but they alone are not capable of preventing bone loss in early menopausal women. A potent anti-resorptive agent given for at least 5 years is warranted. The options are estrogen or a bisphosphonate, both of which have been shown to prevent bone loss in women at the time of menopause.^{4,6} Raloxifene is

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but no corresponding fall in breast cancer incidence after age 69. This led them to conclude that one-third of all cancers detected by mammographic screening were over-diagnosed. They concluded that women cannot make an informed choice on screening unless the level of over-diagnosis is properly explained to them.

A recent US survey [Schwartz, *JAMA* 2004] found unbridled enthusiasm for cancer screening among the lay public because of the prevalent belief that early detection was synonymous with cure. Although only 6% were aware that mammography might detect nonprogressive breast cancer, 56% said they would want to be tested for “pseudodisease” (cancers growing so slowly they would never cause problems). The authors conclude that the public’s enthusiasm for cancer screening stems, in large part, from the success of public health campaigns for widely recommended cancer screening tests. However, they note that these can be misleadingly simple messages that discourage meaningful discussions regarding prudent use of tests. The challenge is to balance messages and reduce the public’s risk for overtesting and overtreatment.

The merits of annual mammography in premenopausal women, as proposed by Buist et al, must be carefully weighed against the negative effect of much higher numbers of recalls for false-positive findings and overdetection of early-stage disease. Physicians need to develop better ways to communicate these shortcomings of mammography to the public.

Andrew M. Kaunitz, MD
Professor and Assistant Chairman
Department of Obstetrics
and Gynecology
University of Florida Health
Science Center
Jacksonville, FL

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not an attractive option because it is a much less potent bone drug than the other options, and has not been documented to prevent bone loss in women immediately after menopause.

The choice of estrogen as the treatment is straightforward if she is experiencing vasomotor symptoms. Even if she is not experiencing vasomotor symptoms, estrogen is still an option since she has entered menopause so early. If she is reluctant to consider estrogen therapy or has contraindications to its use (eg, history of deep vein thrombosis), I would have no qualms about beginning a bisphosphonate—either risedronate 35 mg once weekly or alendronate in doses of 35 or 70 mg once weekly (it is unclear to me that one of these doses of alendronate is preferred in this case).

If the patient takes estrogen, I would reevaluate after 5 years to determine whether she is still experiencing a symptomatic benefit. If she is no longer symptomatic, I would then switch her to a bisphosphonate for 2 to 3 years to protect her from the relatively rapid bone loss that almost inevitably occurs when estrogen therapy is discontinued.⁷ If she is originally treated with a bisphosphonate, I would reevaluate her clinical situation and fracture risk (based on her BMD and other risk factors) after 5 years to determine whether continued bisphosphonate therapy is justified. Although bone loss begins within the first year after discontinuing bisphosphonate therapy in young postmenopausal women, the rate of loss approximates that seen in untreated patients.^{4,5} The rapid “catch-up loss” observed when estrogen is stopped seems not to occur. If her fracture risk at that time warrants continued therapy, we will have more treatment options available in 5 years, including infrequent intravenous bisphosphonate therapy,⁸ anti-RANKL agents⁹ or SERMs more potent than raloxifene.¹⁰

If she is anxious about taking either estrogen or a bisphosphonate, I would be comfortable with her simply using general measures, with the plan to repeat her BMD test after 1 to 2 years. Bone loss will likely be evident, and the decision to begin treatment could be reassessed at that time. Because she is so young, there is little risk in this approach. Much of the bone loss that occurs would be regained if therapy with estrogen or a bisphosphonate is begun at that time.¹¹

Finally, it would be very important to help this young woman have the appropriate view of her skeletal status. I would explain that she has low bone density and that her risk of developing osteoporosis is greater than that of other women her age. However, her current fracture risk is low, and strategies are available to prevent bone loss and bone fragility, protecting her from the consequences of osteoporosis. Certainly, she should not be told that she “has the bones of a 70-year-old”, a statement that is inaccurate since the relationship between bone density and fracture risk is so dependent upon age-related aspects of bone quality.¹² With the appropriate information before her, she can be an active participant in the management decisions.

—Michael R. McClung, MD

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