Treatment Strategies for Patients with Low Bone Mass
The Younger Postmenopausal Female

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Abstract
Estimating an individual’s fracture risk is the most significant factor for determining the need to initiate bone strengthening treatment in the postmenopausal woman. Fracture risk in inversely and most strongly related to an individual’s bone mineral density values, but other factors including age, prior fracture history, body mass index, general health, family history of fractures, corticosteroid use, and smoking history also influence the risk of subsequent fractures. Fracture risk assessment tools such as the World Health Organization’s FRAX tool and the Study of Osteoporotic Fractures Index provide 10- and 5-year fracture probability estimates, respectively, and using these tools can be particularly helpful in assessing the immediate need to initiate treatment in younger postmenopausal women. Perimenopausal and postmenopausal bone loss averages about 1% per year with more annual bone loss occurring in trabecular than cortical bone and during a normal life span such bone loss can exceed 35% of an individual’s bone mass. Younger postmenopausal women with low bone mineral density values, a history of a previous fracture, greater rates of bone loss as measured by bone turnover markers are more likely to need bone strengthening treatment at an earlier age in the postmenopausal period. Treatment measures include adequate amounts of dietary and supplemental calcium and vitamin D, a routine of regular exercises and medications that reduce the rate of new fractures.

Bone is a dynamic tissue that undergoes modeling and remodeling at different times and rates in response to a variety of stimuli throughout an individual’s lifetime. The maximum amount of skeletal mass accrued in an individual is called their peak bone mass and averages about 2,400 grams in females. Gains in peak bone mass are very rapid during adolescence, with at least 90% acquired by the age of 18. Peak bone mass acquisition is largely determined by genetic and hormonal factors, but can be significantly influenced by life style factors, including body weight, dietary habits, smoking, sun exposure, and levels of physical activity.

Peak Bone Mass and Age-Related Bone Loss
Bone loss in both sexes is a normal consequence of aging, with some bone loss beginning as early as the mid-thirties. Most females will then experience a more pronounced bone loss during the early menopausal years before transitioning into a more gradual and sustained rate of bone loss that continues throughout the postmenopausal years. Over a normal life span, females lose, on average, about 35% of their cortical bone and 50% of their trabecular bone.

Postmenopausal and age-related bone loss is influenced by body weight, smoking history, alcohol consumption, physical inactivity, vitamin D deficiency, and genetic factors. At any point during the postmenopausal period, an individual’s bone mass is merely a measure of her peak bone mass minus the amount of bone she has lost. Bone density scores of females who have their first bone density measurement at the onset of menopause, therefore, generally reflect a value close to an individual’s peak bone mass, since these females have not had sufficient time to experience significant menopause-related bone loss. The challenges to maintaining bone mass during early menopause include identifying females at increased short- and intermediate-term risk for

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fracture, identifying females with progressive bone loss (those developing or likely to develop osteoporosis), and recognizing the need to avoid over- and under-treatment of the many females with some degree of low bone mass. Treatment decision strategies for the first decade of menopause should be based on the same individual absolute fracture risk profile that defines the need for therapeutic intervention in older postmenopausal females.

Bone Mass, Bone Loss and Fracture Incidence

Osteoporosis, the most common metabolic bone disorder, affects over 20% of Caucasian American females. Additionally, more than twice that number will have a lesser degree of low bone mass (osteopenia). Developing strategies to identify females in both groups who are most at risk for fracture is an important clinical imperative, with widespread health and socioeconomic ramifications. Postmenopausal bone loss is, of course, progressive in most females, with fracture risk increasing with age and the attendant bone loss that accompanies aging. While bone mineral density (BMD) values are inversely related to fracture incidence, absolute fracture risk is also independently and most strongly modified by age, previous fracture history, and a number of other risk factors. A 70-year-old female with a bone density T score of -2.5 will have twice the estimated fracture risk as a 50-year-old female with the same bone density score.\(^6\) A 50-year-old Caucasian female has a greater than 50% risk of sustaining a fracture during the remainder of her lifetime, with an almost equal percentage of fractures involving the hip, vertebral bodies, and distal forearm.\(^5\) Wrist fractures first increase in frequency in younger postmenopausal females and in this group are an indication for bone density testing. Age-related site-specific fracture events are most common in the distal forearm, femur and hip, vertebra, pelvis, humerus, and clavicle.\(^4\) The incidence of fractures is directly related to an increase in the rate of falls seen among females, beginning as early as late perimenopause, the transitional period when serum estrogen levels first begin to decline.\(^7\)

Clinical Decisions in the First Decade of Menopause

It is estimated that there are about 8 million postmenopausal American females with osteoporosis and perhaps as many as three times that number with osteopenia.\(^8\) While the fracture rates are highest among females with osteoporosis, the greatest number of fractures occurs in the larger pool of those with osteopenia.\(^9\) Identifying those subjects at high short- and intermediate-term absolute fracture risk is important in order to reduce the incidence of fractures in younger postmenopausal females. Fracture assessment tools provide us with some guidance regarding if and when to recommend initiation of bone-strengthening medications, since they are based on a patient’s likelihood of sustaining a fracture over a finite period of time. Additionally, several recent prospective studies have looked at bone mineral status and fracture rates among females in the perimenopausal transition and during the first decade of menopause; the results of these studies allow us to put fracture risk in an age-related perspective.

The National Osteoporosis Risk Assessment (NORA) is a longitudinal observational study involving a cohort of more than 200,000 postmenopausal American females, who were registered from a series of primary care practices in 34 states across the country.\(^10\) There were almost equal numbers of patients 50 to 59 and 60 to 69 years of age as part of the original enrollment set of participants. The NORA results provide information regarding one- and three-year fracture rates in younger and older postmenopausal females, and their relationship to bone density scores and age. The study used a series of different peripheral bone density devices to measure bone density values, and reported fracture rates in postmenopausal females, aged 50 to 64 and 65 and older. Thirty-seven percent of all fractures occurred in younger females, with 1% of that group having a fracture in the first year after study enrollment. Two percent of the older females had a fracture during the first year of the study. Younger females with lower bone density scores had similar relative risks (1.5) of fracture per each standard deviation decrease in BMD. Sixty-nine percent of younger females had normal bone density scores at baseline, compared to 38% of the older females.\(^10\) Over three years, 2.2% of females in the younger age group reported new osteoporotic fractures. Among the group of females who sustained a fracture, a previous fracture was the most important determinant for short-term fracture risk. Females with a prior fracture had a 7.2% fracture risk over three years regardless of their T scores. Females with T scores lesser or equal to -1.1 had a 3.1% three-year fracture risk, and those with self-reported fair to poor health status had a 2.4% fracture risk over the first 36 months of the study.\(^11\)

The Danish Osteoporosis Prevention Study has also provided important information regarding patterns of bone loss and fracture risk during the first 10 years of menopause.\(^12\) The investigators of this report speculated that baseline BMD values could help predict BMD scores 10 years into the future. They found that an individual participant with a baseline BMD T score above -1.4 (femoral neck or lumbar spine, whichever was lower) had a 10-year risk of less than 10% of developing either an osteoporotic BMD or a fracture. Participants with T scores below -1.4 had a 56% risk of sustaining either a fracture or a low BMD, or both. Participants with baseline osteopenia had a 38% chance of progression to clinical or densitometric osteoporosis. The average annual decline in BMD was 0.8% and 0.9% at the lumbar spine and femoral neck, respectively.\(^13\) Nine percent of participants sustained relevant fractures during the follow-up period, with 80% of the fractures being distal forearm fractures, reflecting, again, the increased frequency of this site-specific fracture during early menopause.\(^13\) In the Danish study, only 0.5% and 3.3% of participants had osteoporotic
femoral neck or lumbar spine BMD scores at baseline.\textsuperscript{12}

At a population level, identifying those individuals at significant time-related fracture risk during the first decade of menopause requires analyzing patterns of bone loss among females with osteopenia. It is estimated that about 50% of a female’s lifetime bone loss occurs during this period of time.\textsuperscript{14} Several recent reports have demonstrated that bone loss begins during the perimenopause, the transitional period prior to the onset of menopause. Recker and colleagues followed 75 females older than 46 years of age who at baseline had estradiol and gonadotropin levels in the premenopausal range and continued to have regular menses.\textsuperscript{15} Over the subsequent nine years, 54 females experienced normal menopause, while 21 remained estrogen-replete by using hormone replacement therapy. Spinal bone loss in the nonestrogen users was 5% of baseline over the 3 years prior to menopause and reached about 11% of the baseline value 4 years after menopause. There was a similar pattern of femoral neck bone loss over the 9-year observational period. The investigators were able to determine that menopausal bone loss at the hip and of the total body is caused by both estrogen deprivation and age per se, while spinal bone loss is caused by estrogen deprivation alone. Estradiol levels began to decrease in the year prior to menopause, while gonadotropin levels were elevated at least a year earlier than the beginning of the decline of estradiol.\textsuperscript{15}

The Study of Women’s Health Across the Nation (SWAN), a seven-center longitudinal cohort study of the menopausal transition, which involves multiple ethnic groups, has recently reported its bone density findings in females from five of their study centers.\textsuperscript{16} The investigators observed annual rates of bone loss of about 1.8% to 2.3% (spine) and 1.0% to 1.4% (hip) during the late perimenopause and postmenopausal periods of observation. However, the rates of bone loss were considerably higher in the females in the lowest tertile of body weight, compared to the females in the highest tertile, and observed differences in ethnic groups were largely eliminated when controlled for body weight.\textsuperscript{16} The latter results support the observation that postmenopausal bone loss is more influenced by environmental or modifiable factors than by inherited factors.

The decision to recommend bone-strengthening medication for a postmenopausal female with a decreased bone mass should be based on that individual’s absolute fracture risk as estimated over a finite period of time. Fracture assessment tools such as the World Health Organization’s FRAX\textsuperscript{TM} and the Study of Osteoporotic Fracture (SOF) index provide information that can help physicians define an individual’s short- and intermediate-term fracture risk. Moreover, the FRAX\textsuperscript{TM} program provides treatment recommendations, based on the 10-year likelihood of an individual sustaining a major fracture or a hip fracture. That probability is estimated from the individual’s BMD, age, body mass index (BMI), prior fracture history, parental history of hip fracture, smoking and alcohol history, corticosteroid use, and whether the patient also has rheumatoid arthritis. The FRAX treatment recommendations are based on cost-effectiveness of treatment and are country-specific; for the United States there are separate analyses for Caucasians, Hispanics, Asians, and blacks.\textsuperscript{17} FRAX recommendations suggest initiating treatment when the 10-year risk for a major osteoporotic fracture is equal to or greater than 20% or the hip fracture risk is equal to or greater than 3%. Using the FRAX tool can help a patient understand the statistical estimate of her fracture risk over a ten-year period of time. A 51-year-old healthy, nonsmoking postmenopausal female, with no previous fracture, and a femoral neck T score of -2.2 would only have an 8.5% chance of sustaining a major osteoporotic fracture during the next decade of her life. Such a person can be monitored for further bone loss with periodic BMD scans, rather than be immediately started on bone-strengthening medications.

The question of the utility of bone turnover markers and their effect on clinical decision-making is not addressed by either the FRAX or the SOF 5-year fracture risk tools, since they do not include bone turnover markers as risk factors. These bone biomarkers include assays that measure bone resorption and bone formation and which, if increased, suggest expansion of the “bone resorption space,” a finding characteristic of the early menopause. Clinically, high levels of markers, such as urinary N-telopeptide, particularly if they are reflected by significant declines in BMD through annual scans (“fast bone losers”), may influence the decision to begin anti-resorptive medication.\textsuperscript{18,19}

**Conclusions**

The decision to initiate treatment in females during the first decade of menopause should be based on their absolute fracture risk over a finite period of time and on the need to preserve or increase a low bone mass. It is generally agreed that postmenopausal females with osteoporotic T scores should be treated, but the type of drug and the length of time it should be used will depend on individual risk factors, particularly BMD, prior fracture history, and general health. A treatment strategy for females who need immediate treatment may include initiating an anabolic agent, particularly if the BMD is very low (a circumstance likely indicating that the low bone mass is a result of an inadequate peak bone mass) or the use of a selective estrogen receptor modulator when a female has both low bone mass and an increased risk for invasive breast cancer. Healthy younger postmenopausal females, with only minimally or moderately decreased bone mass and no fracture history, are unlikely to need treatment during the first decade of menopause. It is important to review any history of falls with all patients and to introduce measures to improve balance when necessary. It is also very important to emphasize the need for all postmenopausal females to consume adequate amounts of calcium (at least half of which should be
from food sources) and vitamin D, as well as to encourage patients to engage in regular weightbearing exercises as ways to help maintain healthy and strong bones.

Disclosure Statement
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