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Osteopenia – What it means and when to treat

BY SOPHIE A. JAMAL, MD, PHD, FRCPC

Over the past 10 years, several large trials have established the importance of identifying and treating postmenopausal women with osteoporosis. Osteoporosis is defined as a T score of ≤ -2.5 by bone mineral density (BMD) testing at either the hip (total or femoral neck) or lumbar spine. Osteoporotic fractures are associated with morbidity, mortality, and increased healthcare costs. Several agents such as the bisphosphonates (alendronate and risedronate), the selective estrogen receptor modulator (SERM), raloxifene, and the 1-34 fragment of recombinant human parathyroid hormone (teriparatide) have all been shown to consistently decrease the risk of spine and nonspine fractures by up to 50% among postmenopausal women with osteoporosis.¹ Based on data from these large trials, combined with the negative health effects of osteoporotic fractures, clinical practice guidelines from both North America and Europe have consistently recommended pharmacologic treatment in postmenopausal women with osteoporosis.^{2,7}

Despite the significant advances in the treatment of postmenopausal osteoporosis, the approach to managing postmenopausal osteopenia (ie, a BMD T-score between -1 and -2.5 at the hip or lumbar spine) remains unclear. For example, should all women with osteopenia be treated with pharmacologic therapy? If not, what criteria should clinicians use to decide which women with osteopenia should receive treatment? An evidence-based approach to the management of postmenopausal women with osteopenia is discussed in this issue of *Endocrinology Rounds*.

The Case

Mrs. Smith is a 52-year-old woman who is 2 years postmenopausal. She was prompted to have a BMD test when her mother, who is 95-years-old, slipped on ice and fractured her hip. She comes to your office with a copy of her BMD results. Mrs. Smith is very concerned because the report states that she has "osteopenia" at the lumbar spine. She wants to know what treatment you would recommend.

Mrs. Smith feels well, has not had any medical illnesses, and has never had a fracture. Her diet includes 4 dairy servings a day (note that one dairy serving is equivalent to about 300 mg of elemental calcium) and she takes a multivitamin that has 400 IU of vitamin D. She is not taking any medications and has never used oral glucocorticoids. She does not smoke or drink alcohol. Her physical examination is normal. You review her BMD report and the T score at the lumbar spine is -1.4 and the T score at the total hip is -0.8.

How to interpret the BMD report

BMD results are reported using two terms: the T score and the Z score. Both terms rely on a standard deviation (SD) for measurement. An SD represents the



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normal variability of a measurement in a population; the distance between the 5th and 95th percentile of a group covers about 4 SDs. For hip and spine BMD, 1 SD corresponds to about 10% to 15% of the mean value.

- The **Z score** is the number of SDs below (minus) or above (plus) the mean value for people of the same age. For example, a Z score of “0” means that the patient has a value that is exactly at the mean for his or her age. A Z score of -2.0 at the spine means that the patient has a BMD value at the spine that is 2 SDs below the mean value of others who are the same age.
- The **T score** is the number of SDs below the mean value of BMD for young (20- to 30-year-old) adults. A T score of “0” means that the patient’s BMD value is exactly at the mean for young adults. A T score of -2.5 at the spine means that the patient has a BMD value that is 2.5 SDs below the average value found in healthy 20- to 30-year-olds.

Low BMD is strongly associated with an increased risk of fractures in postmenopausal women. The relationship between BMD and fracture risk is customarily quantified by the “relative risk per SD decrease in BMD.” For example, a relative risk to SD ratio (RR/SD) of 1.5 means that a woman whose BMD is 1 SD below the mean for her age has a 50% higher fracture risk than a woman whose BMD is average for her age. Among postmenopausal Caucasian women, the relationship between hip BMD and hip fracture is about 2.6 RR/SD.⁸

Despite these performance characteristics, it should be recognized that just because the BMD is normal, there is no guarantee that a fracture will not occur since it is only the risk that is decreased. Indeed, as discussed below (see Osteopenia – Putting it in Context), most fractures occur in patients *without* osteoporosis.^{9,10} Conversely, if the BMD is in the osteoporotic range, then fractures are more likely, but are not inevitable.¹¹ One explanation for the “disconnect” between BMD values and fractures is that BMD only captures one component of fracture risk – specifically bone quantity – and other factors such as bone quality and risk of falling also contribute to fracture risk independently of BMD (see the section about when to treat women with osteopenia).

Diagnosing osteoporosis

In 1992, the World Health Organization (WHO) defined osteoporosis as a T score of -2.5 or lower at any site of measurement.¹⁰ This cut-off is rather arbitrary.

It was designed to compare the prevalence of osteoporosis in different countries, not to aid in the care of individual patients. However, as discussed earlier, all practice guidelines, including the recently published 2002 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada, recommend drug treatment for postmenopausal women with T scores at either the hip or spine of ≤ -2.5 .¹²

Osteopenia – Putting it into context

Occasionally, patients such as Mrs. Smith and their physicians are unnecessarily distressed when they receive a report stating that they have osteopenia. Osteopenia is neither a cause for alarm nor a reason to start treatment. Osteopenia was defined by a WHO conference as “a BMD T score between -1.0 and -2.5.” The upper end of the range, ie, a T score of -1.0, was decided arbitrarily to indicate women whose BMD was below normal for young adults. About half of all postmenopausal women have a BMD value in this range and could be labeled as having osteopenia. To expand this concept further, because there are more women with osteopenia than osteoporosis, it follows that a greater proportion of osteopenic women will have fractures than osteoporotic women. For example, data from the Geelong Osteoporosis Study, a large observational study in Australia, reported that 54.2% of subjects with osteopenia had fractures, whereas only 28.8% of subjects with osteoporosis had fractures.¹³

Despite this, physicians should not initiate drug treatment based only on the presence of osteopenia. Rather, treatment recommendations should be based on additional risk factors for fracture and the benefits of treatment at various levels of BMD. Indeed, although bone mass is an important contributor to fracture, other abnormalities of the skeleton may contribute to fracture independently of BMD. One example of this is poor bone quality. Bone quality cannot be measured directly, but a prior low trauma fracture in the setting of only a modestly decreased BMD is a good indicator of poor bone quality. Furthermore, other nonskeletal factors, such as an increased risk of falling and the force of impact, contribute to falling risk.

Age and fracture risk

One factor that is associated with an increased risk of fracture is increasing age. For any given T score, fracture risk is much higher in the elderly than in the young.¹⁴ This is because age contributes to

Table 1: Estimated 5-year risk (%) of various types of fractures for white women at various ages and femoral neck T scores²²

Femoral neck BMD T score								
Age	-3.5	-3.0	-2.5	-2.0	-1.5	-1.0	-0.5	0.0
Any low trauma fracture (excluding vertebral fracture)								
50	15	12	10	9	7	6	5	4
60	19	16	14	12	10	8	7	6
70	25	21	18	16	13	11	9	8
80	32	28	24	20	17	15	12	10
Vertebral fracture								
50	5	3	2.4	1.8	1.3	0.9	0.7	0.5
60	8	6	4	3	2.2	1.6	1.2	0.9
70	13	10	7	5	4	3	2	1.5
80	22	16	12	9	7	5	4	3
Hip fracture								
50	1.5	0.9	0.5	0.3	0.2	0.1	0.1	<0.1
60	3.2	1.9	1.2	0.7	0.4	0.3	0.2	0.1
70	7	4	2.5	1.5	0.9	0.6	0.3	0.2
80	13	9	5	3	2	1.2	0.7	0.4

fracture risk independently of BMD. Indeed, from our knowledge about the relationship between BMD and fracture risk, it would be predicted that hip fracture risk might increase 4-fold between the ages of 50 and 80 years. In reality, however, the hip fracture risk increases 30-fold, indicating that, over a lifetime, changes in age are approximately 7-fold more important than changes in BMD. The relationship between age, BMD, and the 5-year risk of fracture at various sites are given in Table 1. For example, the estimated 5-year risk of any nonspine low trauma fracture in a 50-year-old woman with a T score of -2.5 at the femoral neck is 10% and this increases to 24% for an 80-year-old woman with the same T score (Table 1).

Treating osteopenia – A qualitative analysis

There are several methods for evaluating the effectiveness of treating women with osteopenia. Included in these methods is the number needed to treat (NNT), which is relevant to clinicians, and the cost-effectiveness analysis, which may be particularly relevant to health policy-makers. If we consider the NNT; among postmenopausal women with BMD T scores below -2.5 (consistent with osteopenia), approximately 20 women would need to be treated to prevent one spine fracture. In contrast, among postmenopausal women with BMD T scores between -1.6 and -2.5, approximately 200 women would need to be treated to prevent one spine fracture.

Cost-effective analysis is a formal method of assessing the costs and the health effects of an inter-

Table 2: The cost in quality adjusted life year saved with a strategy of 5 years of alendronate therapy compared to no therapy¹⁵

Age	Femoral neck T score		
	-1.0	-1.5	-2.0
50	\$258,609	\$196,138	\$135,161
55	\$211,178	\$150,896	\$100,379
60	\$183,161	\$129,756	\$85,676

vention. A cost-effective analysis asks, “How much extra health do you get for \$1 spent?” Typically, it is expressed in dollars spent per quality-adjusted life years (QALYs) gained. A recent study calculated the cost per QALY gained (cost-effectiveness ratio) based on treatment for 5 years with the bisphosphonate, alendronate, in osteopenic women.¹⁵ This study reported that treating otherwise healthy osteopenic women, ranging in age from 50 to 60 years, is *not* cost-effective. Even among older women with low BMD T scores, drug treatment is *not* cost-effective. For example, giving alendronate for 5 years to a 60-year-old postmenopausal woman with a BMD T score of -2.0 at the femoral neck costs \$85,676 per QALY saved compared to no treatment (Table 2). This is a higher cost-effectiveness ratio than in the most commonly used medical interventions (typically \$50,000 per QALY). These data suggest that recommendations for treating women with osteopenia should *not* be based solely on age or BMD T score.

When to treat women with osteopenia

If, as discussed above, we should not base treatment decisions solely on BMD or even age, what criteria should we use to decide on therapy for postmenopausal women with osteopenia? A reasonable approach is to consider factors that contribute to fracture risk over and above that provided by BMD measurements or age. Many clinical risk factors for osteoporotic fractures have been identified (Table 3). Some of these risk factors warrant particular emphasis and are discussed below.

Many studies indicate that a history of fragility fracture (clinical low trauma fractures or vertebral fractures on X-ray) is an important risk factor for further fracture. Fracture risk is approximately doubled in the presence of a prior fracture.¹⁶ The increase in risk is even more marked for a vertebral fracture following a previous spine fracture. For example, the presence of ≥ 2 prevalent vertebral fractures is associated with a 12-fold increase risk in fracture for any given BMD.¹⁷

Table 3: Major and minor risk factors for osteoporotic fracture¹²

Major risk factors	Minor risk factors
<ul style="list-style-type: none">• Age > 65 years• Vertebral compression fracture• Fragility fracture after age 40• Family history of osteoporotic fracture (especially maternal hip fracture)• Systemic glucocorticoid therapy for >3 months• Malabsorption syndrome• Primary hyperparathyroidism• Propensity to fall• Osteopenia apparent on x-ray film• Hypogonadism• Early menopause (before age 45)	<ul style="list-style-type: none">• Rheumatoid arthritis• History of clinical hyperthyroidism• Chronic anticonvulsant therapy• Low dietary calcium intake• Smoker• Excessive alcohol intake• Excessive caffeine intake• Weight <57 kg• Weight loss >10% of weight at age 25• Chronic heparin therapy

Glucocorticoids are an important cause of osteoporosis and fractures.^{18,19} Bone loss is believed to be the most rapid in the first few months of glucocorticoid treatment and is most marked at the spine, where cancellous bone predominates. The fracture risk conferred by the use of corticosteroids is, however, not solely dependent on bone loss and BMD-independent risks have been identified. These risks include low BMI (<25 kg/m²), prior fracture after 50 years, parental history of hip fracture, current smoking, rheumatoid arthritis, and alcohol intake of >2 units per day. Low BMI is a well-recognized risk factor for fractures and is most marked in lean individuals with a BMI <20 kg/m². Above 20 kg/m², increments in weight have little protective effect, so that leanness is the risk factor rather than obesity being a protective factor. The association between fracture risk and leanness is largely dependent on BMD. For example, in the case of hip fracture risk, only a modest risk persists after adjustment for BMD.²⁰

How should these risk factors guide treatment decisions in postmenopausal women with osteopenia? The 2002 Canadian Medical Association Clinical Practice Guidelines recommend physicians consider therapy for postmenopausal women who have a T score of less than -1.5 at the hip or spine AND:

- a personal history of low trauma fractures after age 40 years
- the presence of vertebral fractures on x-ray (confirmed by history to be low trauma)
- the presence of 1 major or 2 minor risk factors (Table 3).¹²

These recommendations are based primarily on consensus rather than clinical trial evidence.

Recently, data from the National Osteoporosis Risk Assessment (NORA) cohort was utilized to identify risk factors associated with the short-term risk of fracture in osteopenic women. Factors associated with an increased risk of fracture include: a prior low trauma fracture, a BMD T score of ≤ 1.8 , a fair or poor self-reported health status, or poor self-reported mobility.²¹ Note that the risk factors identified in the NORA cohort take into account bone quality (a prior low trauma fracture), bone quantity (the low BMD T score), and the risk of falling (the poor self-reported health status and mobility). The authors suggest that these factors should guide treatment decisions in osteopenic women.

Summary and treatment recommendations for Mrs. Smith

Mrs. Smith is a 52-year-old postmenopausal woman with osteopenia, her BMD T score is -1.4 at the lumbar spine and -0.8 at the total hip. Regardless of the BMD result, Mrs. Smith should be advised to obtain an adequate intake of dietary calcium (1500 mg/day, including supplements if necessary) and vitamin D (800 IU/day). We would also recommend that she participate in lifelong regular weight-bearing exercise and muscle-strengthening exercises to reduce the risk of falls and fractures.

With regards to pharmacologic therapy, based on a review of the available data, it would seem reasonable to recommend pharmacologic therapy to Mrs. Smith if she had a prior low trauma

Table 4: Approach to management of postmenopausal women with osteopenia

General recommendations

- Calcium 1500 mg/day
- Vitamin D 800 IU/day
- Lifelong regular weight-bearing and muscle strengthening exercise

Pharmacologic therapy

- Prescribe pharmacologic therapy in women with a prior low trauma fracture
- Consider pharmacologic therapy in women with T scores less than -1.5 who have other risk factors for fracture, including risk factors for falls.
- Take into account rates of bone loss, largely dictated by years since menopause, when considering pharmacologic therapy.

fracture (including a “silent” vertebral fracture). Pharmacologic therapy could also be considered if the BMD T score at either the hip or spine was lower than -1.5 and there were a number of clinical risk factors for fracture (Table 3). Another factor to consider in the latter scenario is the rate of bone loss. Recall that a 1 SD decrease in BMD at any site (eg, from -1.5 to -2.5) is equivalent to approximately 10% bone loss. In the first 3 to 5 years after menopause, the average bone loss is approximately 2% per year, but some women – so called “fast losers” – can lose 4% to 5% per year. After the first 5 years following menopause, in otherwise healthy women, bone loss is about 0.5 to 1.0% per year (Table 4).

However, Mrs. Smith has not had a prior low trauma fracture, is 2 years postmenopausal and, although she has a maternal history of hip fracture, has no other major or minor risk factors for fracture and, as such, is at low risk for osteoporotic fractures. She is in good health and does not have impaired mobility, thus, she is at low risk for falling. Recall that her lumbar spine BMD T score is -1.4 and, even if she lost 5% over the next year, her BMD would still be in the osteopenic range (T score of -1.9). Based on these data, we elected NOT to prescribe pharmacologic therapy to Mrs. Smith. Although, as mentioned above, she should take supplemental calcium and vitamin D and do regular weight-bearing exercise. We will see her in the clinic in one year for a repeat BMD.

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Abstracts of Interest

Fracture Burden Contributed by Women With Osteopenia: Geelong Osteoporosis Study

PASCO JA, HENRY MJ, MERRIMAN EN, NICHOLSON GC, SEEMAN E, KOTOWICZ MA. AUSTRALIA.

The purpose of this study was to quantify fracture risk associated with normal, osteopenic and osteoporotic areal bone mineral density (BMD) based on WHO criteria. This prospective analysis follows 628 postmenopausal women (median age 74.0 yr, range 60-94) who had BMD assessments 1994-7. 37.1% had normal BMD at the total hip, 48.2% were osteopenic and 14.8% osteoporotic. Subjects were followed until the end of 2002, or until sustaining a fracture, death, or migration from the study region. Post-baseline fractures were identified radiologically. During the study period 66 women died, 25 left the region, 144 sustained at least one fracture and 393 remained fracture-free, alive and residing in the region, generating 3220 person years of follow-up. After 5 years, the proportion of fractures occurring in each category of BMD was 17.0% normal, 54.2% osteopenia and 28.8% osteoporosis. Using Cox proportional hazards models, both decreasing BMD and increasing age contributed independently to increased fracture risk. Categorizing age into groups 60-69, 70-79 and 80+ yr, and setting 60-69 yr with normal BMD as the referent group, relative risk (RR) for fracture for the osteopenic women was 2.7 (95%CI 1.1-6.6) for 60-69 yr, 4.7 (2.1-10.9) for 70-79 yr and 6.1 (2.7-14.1) for 80+ yr; RRs for the osteoporotic women were 6.1 (1.8-20.8), 6.2 (2.3-16.8) and 9.3 (4.0-21.8), respectively (all $p < 0.05$). Thus, osteoporotic women have the greatest risk for fracture and this risk increases with age. The RR for fracture among osteopenic women is intermediate between osteoporotic and normal women. Although women with osteoporotic BMD are at greater risk for fracture, they contribute less than a third to the total burden of fractures occurring in the community. Over half of the fractures arise from women with BMD in the osteopenic range who represent approximately 50% of the population at risk.

Abstract SU378 at the 26th Annual Meeting of the American Society for Bone and Mineral Research, October 1-5, 2004 Seattle, Washington

Drug Therapy For Early Post-menopausal Osteopenic Women in the Absence of Prior Fracture is NOT Cost-Effective

SCHOUSBOE JT, ENSRUD KE, NYMAN JA, KANE RL, MELTON LJ. MINNEAPOLIS, MN, ROCHESTER, MN.

Some drugs are FDA approved to prevent bone loss in osteopenic (spine or hip T-score between -1.0 and -2.5) post-menopausal women, and are currently being marketed for that indication by industry. In the absence of prior fracture, osteopenic women are not at high risk of fracture. Targeting healthy women at the menopause may be especially problematic. To evaluate this issue, we used a Markov model with seven health states (No Fracture, Wrist, Clinical Vertebral, Hip, Vertebral and Hip, Other Fractures, and Death) to estimate the incremental lifetime costs and health benefits of a strategy of alendronate therapy for five years compared to no drug therapy in osteopenic early post-menopausal women. "Other" fractures included distal femur, humerus, proximal radius, pelvis, rib, and fibula/tibial fractures. Fracture rates, direct medical costs of fracture, and long-term care costs after hip fracture were derived from comprehensive population-based data of Rochester, MN. We assumed 1) the worst estimates for loss of quality of life from

fracture published in the medical literature, 2) a 50% reduction in vertebral and 34% reduction in non-vertebral fractures with alendronate therapy in the no fracture state, 3) a 50% reduction in all fractures with alendronate therapy after any incident fracture, 4) discount rates of 3% for costs and health benefits, 5) alendronate cost equal to U.S. average wholesale price for 2001, and 6) gradual offset of fracture reduction benefit over 5 years after alendronate discontinuation. The table below shows the incremental cost (in 2001 US \$) per quality adjusted life-year saved with this strategy compared to no drug therapy, from Monte Carlo simulations (20,000 trials each) of the model.

Age	Femoral Neck T-Score		
	-1.0	-1.5	-2.0
50	\$258,609	\$196,138	\$135,161
55	\$211,178	\$150,896	\$100,379
60	\$183,161	\$129,756	\$85,676

These results are insensitive to varying fracture rates or costs by 30%. Even assuming a very high societal willingness to pay of \$100,000 per QALY saved and best case scenario regarding drug efficacy, alendronate therapy for healthy osteopenic early post-menopausal women who have not had a fracture is not cost-effective. These results are highly likely to be applicable to other anti-resorptive drugs, since they are similar in cost to and no more efficacious in preventing fracture than alendronate.

Abstract F402 at the 26th Annual Meeting of the American Society for Bone and Mineral Research, October 1-5, 2004 Seattle, Washington

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