CLINICAL PRACTICE

Osteopenia

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 55-year-old asymptomatic woman, who is 5 years postmenopausal, is concerned about osteoporosis, since her mother had a hip fracture at the age of 70 years. The patient has no personal history of fractures and has never taken corticosteroids. She does not smoke but does drink one to two glasses of wine a day. Her weight is 105 lb (48 kg), and her height is 62 in. (1.6 m); she has a body-mass index (the weight in kilograms divided by the square of the height in meters) of 19.2. Measurements of bone mineral density with the use of dual-energy x-ray absorptiometry show T scores of –1.7 at the spine and –1.5 at the femoral neck, findings that are consistent with osteopenia. What should you advise?

THE CLINICAL PROBLEM

It has long been known that fractures in elderly persons are associated with bone fragility,[1] but not until the advent of bone densitometry has that assessment been standardized.[2] Bone mineral density (expressed in grams per square centimeter) is a better predictor of fractures than blood pressure is of stroke, with a relative risk of hip fracture of 2.6 for each 1 SD decrease in bone mineral density at the hip.[3] Like the relation between blood pressure and the risk of stroke, the relation between bone mineral density and the risk of fracture is continuous, with no absolute cutoff value to define a pathologic state. According to a working group of the World Health Organization (WHO), osteoporosis is defined as a T score of –2.5 or lower (i.e., bone mineral density that is 2.5 SD or more below the normal mean value for young adults), and osteopenia as a T score that is higher than –2.5 but less than –1.0 (Table 1).[4]

By this criterion, an estimated 33.6 million Americans — 80% of them women — have osteopenia.[5] The value of labeling such patients, whose bone mineral density may be within the normal range, has been questioned,[6] but osteopenia is analogous to prehypertension,[7] impaired fasting glucose,[8] and borderline high cholesterol[9] in defining an intermediate-risk group with somewhat uncertain boundaries. Although the risk of fracture is greater among patients with osteoporosis than among those with osteopenia, the much larger number of persons with osteopenia means that this group represents a substantial portion of the population at risk for fracture. For example, in the National Osteoporosis Risk Assessment Study,[10] which involved 149,524 postmenopausal white women recruited from primary care practices who were followed for 1 year, there were so many more women with osteopenia than with osteoporosis (39% vs. 6%) that the number of fractures observed was greater among those with osteopenia (Fig. 1).

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Table 1. WHO Diagnostic Categories of Bone Mineral Density.*

Diagnostic Category	Criterion
Normal	A value for BMD or BMC that is within 1.0 SD of the reference mean for young adults
Low bone mass (osteopenia)	A value for BMD or BMC that is more than 1.0 but less than 2.5 SD below the mean for young adults
Osteoporosis	A value for BMD or BMC that is 2.5 SD or more below the mean for young adults
Severe osteoporosis (established osteoporosis)	A value for BMD or BMC that is 2.5 SD or more below the mean for young adults in combination with one or more fragility (low-trauma) fractures.

* The information is from the WHO.[4] BMD denotes bone mineral density, and BMC bone mineral content.

STRATEGIES AND EVIDENCE

The clinical dilemma posed by osteopenia typically arises when bone mineral density tests are ordered for patients without an obvious indication for osteoporosis treatment, such as a clinically evident vertebral fracture.[11] This problem can be mitigated by following recommendations for osteoporosis screening delineated in a previous review in the *Journal*[12] — for example, testing persons who are 65 years of age or older and those who have risk factors for bone loss or falls, as summarized in Table 2. Such screening helps identify a population of patients whose risk of fracture is sufficiently great that therapy is viewed as cost-effective,[13] an important consideration, given the large number of people with osteopenia. It has also been suggested that attention should be focused on the lower part of the osteopenic range (e.g., using a T score below –2.0 to identify those at risk, as is done in many clinical trials, rather than a T score below –2.5, the cutoff for the diagnosis of osteoporosis). Although this approach would identify a greater percentage of the at-risk population, it would also result in the evaluation and treatment of more people who have a low risk of fracture.

Effective fracture prediction can be improved, however, by combining measurements of bone mineral density with clinical risk factors.[14] A WHO working group was established in 2004 to define a set of clinical risk factors that would be easy to assess in primary care practice and would predict the risk of fracture (independently of bone mineral density) in both sexes, various ethnic groups, and various geographic regions.[15] Combining data from large community-cohort studies (60,161 subjects followed for 254,582 person-years, with 5563 fractures observed), the group identified a number of robust clinical risk factors.[16] Table 3 shows the relative risk of hip fracture associated with each clinical risk factor, after adjustment for age and bone mineral density. In conjunction with measurements of bone mineral density, these factors could be used to estimate the likelihood of an osteoporotic fracture, just as the risk scores in the Framingham Heart Study are used to predict the relative risk of heart disease.[17] Algorithms that incorporate these risk factors along with measurements of bone mineral density and age are being developed to calculate 10-year absolute probabilities of fracture among white and nonwhite women and men in the United States.

ADDITIONAL TESTING

Additional testing may help identify patients with osteopenia who are at increased risk for fracture as compared with others with similar values for bone mineral density.

Assessment for Vertebral Fractures

The single best predictor of fractures is a previous osteoporotic fracture,[18] but vertebral fractures may not be clinically apparent.[19] In asymptomatic patients with osteopenia, radiography is thus a useful tool for uncovering any unrecognized vertebral fractures.[20] Given its cost and the radiation exposure, however, a good alternative is vertebral-fracture assessment with the use of dual-energy x-ray absorptiometry,[21] which is cheaper and requires less radiation. Use of dual-energy x-ray absorptiometry to detect vertebral factures involves obtaining images of the lateral spine and requires a newer machine with this capability, special software, and specially trained technicians. The sensitivity and specificity of vertebral-fracture assessment for detecting moderate or severe fractures, with spinal radiographs used as the gold standard, are estimated to be 87 to 93%, and 93 to 95%, respectively.[21] Thus, dual-energy x-ray absorptiometry combined with vertebral-fracture assessment may be a relatively cost-effective way to identify unrecognized vertebral fractures in otherwise asymptomatic patients with osteopenia.[21]

Markers of Bone Turnover

Another possible approach to identifying patients with osteopenia who have accelerated bone loss is to measure biochemical markers of bone turnover. Since bone resorption and bone formation

are coupled processes, markers of resorption (urinary or serum C-terminal and N-terminal cross-linked telopeptides of type I collagen) and formation (bone-specific alkaline phosphatase, osteocalcin, and N-terminal propeptide of type I collagen) can be used to assess the rate of bone remodeling.[22] In population-based studies, increased bone turnover is associated with an increased risk of fracture, independently of bone mineral density, and with a higher likelihood of accelerated bone loss.[23] However, the usefulness of bone-turnover markers in improving the ability to predict fracture risk in individual patients has been hampered by biologic and assay variability,[24] and the routine use of these markers in the evaluation of patients with osteopenia cannot be recommended at this time.

Other laboratory testing in patients with osteopenia should be dictated by clinical judgment.[25] Serum calcium and phosphorus levels and tests of renal and hepatic function may be warranted in some cases, and measurement of thyroid-stimulating hormone may identify women with hyperthyroidism that is not clinically obvious. Some clinicians perform more aggressive laboratory evaluation in patients with values for bone mineral density that are 2 SD or more below the mean value for women of the same age (i.e., a z score of –2 or or lower). Given the increasing recognition that vitamin D deficiency (a 25-hydroxyvitamin D level below 15 ng per milliliter [37 nmol per liter]) and insufficiency (a 25-hydroxyvitamin D below 25 to 30 ng per milliliter [62 to 75 nmol per liter]) are common in postmenopausal women and may contribute to bone loss,[26] serum 25-hydroxyvitamin D levels should be measured with a reliable assay. Vitamin D deficiency should be treated before initiating pharmacologic therapy.

WATCHFUL WAITING VERSUS PHARMACOLOGIC INTERVENTION

After excluding possible secondary causes of bone loss, the clinician must decide whether to recommend appropriate lifestyle changes and then reassess bone mineral density at a follow-up visit (typically in 1 to 3 years) or to initiate pharmacologic therapy in addition to lifestyle modifications.

Lifestyle Modifications

Table 4 lists the standard lifestyle interventions generally recommended for patients with osteopenia. A total intake of 1200 to 1500 mg of calcium per day (through diet, supplements, or both) and 400 to 800 IU of vitamin D per day is recommended for all postmenopausal women. A recent meta-analysis of 15 trials involving postmenopausal women showed that calcium supplementation (500 to 2000 mg daily) had small but significant favorable effects on bone mineral density at various sites (approximately a 2% increase over a period of 2 or more years), with a trend toward a reduction in vertebral fractures but no measurable effect on non-

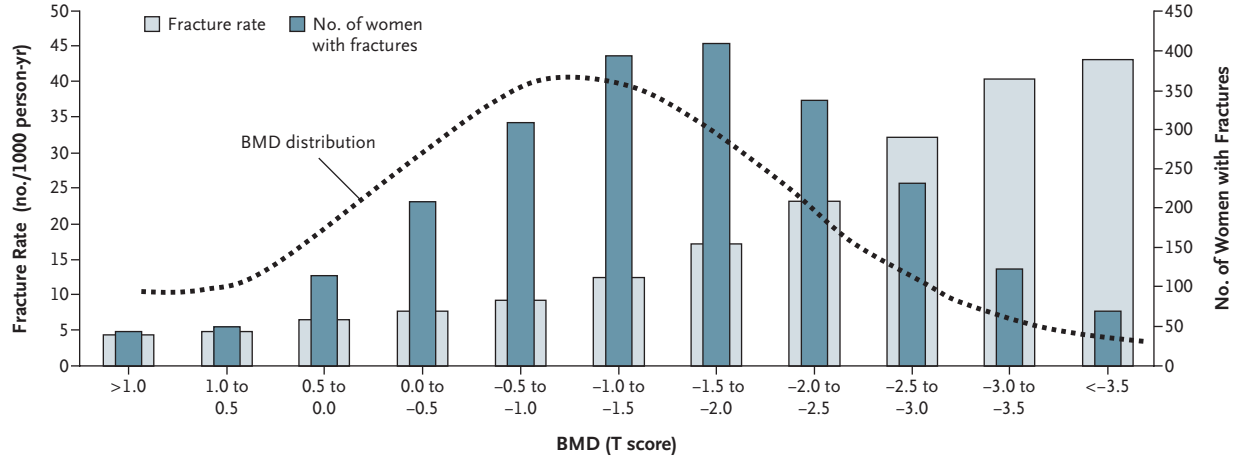

Figure 1. Fracture Rate and the Number of Women with Fractures According to Peripheral Bone Mineral Density (BMD).
Data are from Siris et al.[10]

Table 2. Risk Factors for Osteoporosis and Fracture in White Postmenopausal Women.*

Major risk factors
Personal history of fracture as an adult
History of fragility fracture in a first-degree relative
Low body weight†
Current smoking
Use of oral corticosteroid therapy (daily dose equivalent, ≥5 mg of prednisone) for more than 3 months
Additional risk factors
Impaired vision
Estrogen deficiency at an early age (before 45 years)
Dementia
Poor health or frailty
Recent falls
Low calcium intake (lifelong)
Low physical activity
Alcohol in amounts greater than two drinks per day

* The information is from the National Osteoporosis Foundation.[11]
† Low body weight is defined as a weight below 127 lb (58 kg), which is based on the lowest quartile for weight of the cohort in the Study of Osteoporotic Fractures, but the definition varies among populations.

vertebral fractures.[27] Similarly, a meta-analysis of 25 trials involving postmenopausal women showed that vitamin D supplementation (300 to 2000 IU daily) reduced the risk of vertebral fractures, with a trend toward reduced nonvertebral fractures,[28] although heterogeneous studies were analyzed, including many involving elderly women with clinically significant vitamin D deficiency. Recent data from the Women's Health Initiative (WHI) in healthy postmenopausal women with baseline calcium and vitamin D intakes of approximately 1150 mg and 360 IU per day, respectively, showed that calcium and vitamin D supplementation (1000 mg and 400 IU, respectively), as compared with placebo, resulted in a small but significant increase in bone mineral density at the hip (1.06%), but did not significantly reduce hip fracture (the primary outcome) and increased the risk of kidney stones.[29] However, since the mean calcium and vitamin D intakes in the placebo group were close to the currently recommended ranges, these data do not negate current recommendations for calcium and vitamin D intake.

Weight-bearing exercise is also recommended for the prevention of osteoporosis. A meta-analysis of 15 short-term trials (6 to 24 months) examining the effects of various supervised upper- and lower-body loading exercises, performed three to five times per week, on rates of bone loss in postmenopausal women[30] concluded that such exercises modestly improved bone density. As compared with changes in control subjects, resistance training resulted in small increases in bone mineral density at the spine (mean increase, 0.006 g per square centimeter), with inconsistent findings for bone mineral density at the hip. Similarly, a meta-analysis of 10 trials showed that walking (90 to 280 minutes per week, generally divided into three to five sessions) had a small but significant effect on bone mineral density at the spine but not at the femur.[31]

Pharmacologic Therapy

The Food and Drug Administration has approved a number of drugs for the prevention of postmenopausal osteoporosis, including bisphosphonates (alendronate, risedronate, and ibandronate), a selective estrogen-receptor modulator (raloxifene), and oral or transdermal estrogens (Table 5). All of these agents attenuate ongoing bone loss,[32-36] but there are limited data regarding their efficacy in reducing the risk of fracture in women with osteopenia. Although most clinical trials with fracture outcomes have involved women with T scores of –2.0 or less or women with prevalent vertebral fractures,[32-35] trials of raloxifene[37] and alendronate[38] have shown a reduction of approximately 50% in the risk of vertebral fractures specifically in women with osteopenia. However, the data are conflicting; another trial[39] failed to find a significant effect of alendronate on clinical fractures (vertebral and nonvertebral) in women with T scores above –2.5. The WHI trial showed that estrogen–progestin therapy reduced hip fractures by 33% and reduced all fractures by 24% in the population of women studied. On the basis of measurements of bone mineral density performed in approximately 6% of the WHI study population, most of the women had osteopenia or normal bone mineral density rather than osteoporosis[40]; whether the reduction in fracture risk occurred primarily in the subgroup of women (approximately 5%) with T scores below –2.5 rather than in the women with osteopenia is unclear. Furthermore, the increased risks associated with postmenopausal hormone use (including breast cancer, cardiovascular events, and dementia in older women) were considered to outweigh

the benefits for bone, and other nonestrogen therapies are preferred when pharmacologic therapy is used.

Moreover, it is important to note that even a 50% relative reduction in the risk of fracture would have only a modest effect on the absolute fracture risk for the majority of women with osteopenia. For example, in an average 55-year-old woman with a T score of –1.5, pharmacologic therapy would be expected to reduce the estimated 10-year risk of fracture associated with osteoporosis from 8 to 4%,[41] and this may not represent a cost-effective use of health care resources.[42]

Decisions regarding pharmacologic therapy must take into account the long period of treatment (generally prescribed for at least 5 to 10 years and sometimes indefinitely) and its substantial costs and potential side effects. Certain additional risk factors for fracture (e.g., documented vertebral fractures or prolonged use of glucocorticoid therapy) would clearly warrant pharmacologic therapy. In the absence of such compelling indications, counseling combined with follow-up assessment of bone mineral density is a reasonable strategy. If follow-up testing shows decreases in bone mineral density that exceed those reflecting the variability that is attributable to the measuring equipment (i.e., greater than the least significant change,[43] which is generally a change of more than 3 to 4%), pharmacologic therapy can be considered for prevention of further bone loss. Therapy should be instituted if the values on follow-up testing are in the osteoporotic range.

Table 3. Relative Risk of Hip Fracture According to Key Clinical Risk Factors after Adjustment for Age and Bone Mineral Density.*

Risk Factor	Relative Risk (95% CI)
Prior fracture after age 50 yr	1.62 (1.30–2.01)
Body-mass index (20 vs. 25)	1.42 (1.23–1.65)
Previous or current use of systemic corticosteroids	2.25 (1.60–3.15)
Rheumatoid arthritis	1.73 (0.94–3.20)
Parental history of hip fracture	2.28 (1.48–3.51)
Current smoking	1.60 (1.27–2.02)
Alcohol intake >2 drinks daily	1.70 (1.20–2.42)

* Data are from Kanis et al.[16] Body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 4. Lifestyle Measures Recommended for Patients with Osteopenia.

Adequate weight-bearing exercise (e.g., walking, moderate resistance training)
Smoking cessation
Avoidance of excessive alcohol intake (no more than two drinks/day)
Calcium supplementation to a total intake of 1200–1500 mg/day for all postmenopausal women and for men over the age of 65 years
Vitamin D supplementation (400 to 800 IU/day) to achieve a serum 25-hydroxyvitamin D concentration >25–30 ng/ml*

* Although some experts have advocated higher doses of vitamin D for possible nonskeletal benefits (e.g., cancer prevention), the efficacy and long-term safety of higher doses remain to be established. Depending on the serum 25-hydroxyvitamin D concentration, higher doses of vitamin D may be necessary to replete vitamin D stores.

AREAS OF UNCERTAINTY

As discussed above, a key unresolved area is the ability to distinguish between women with osteopenia in whom antiresorptive therapy is warranted and those in whom lifestyle interventions are sufficient. An additional area of uncertainty is the relevance of bone mineral density at sites other than the hip in assessing fracture risk. The original definition of osteopenia by the WHO was based on measurements of bone mineral density at the hip in white women.[44] Bone mineral density at the spine is also often measured, since this assessment may result in better detection of early postmenopausal bone loss,[12] but its predictive value for fracture has been less well studied. Discrepancies in the apparent prevalence of osteopenia (as compared with that defined by hip bone mineral density) also arise when the T-score definitions are extended to include measurements of bone mineral density made with the use of techniques other than dual-energy x-ray absorptiometry (e.g., ultrasonography or computed tomography), at peripheral skeletal sites,[45] or in patients who are members of minority groups[46] (who have not been well studied[47-49]). Although this review focuses on postmenopausal women with osteopenia, there are even greater uncertainties in diagnosis and management among men and premenopausal women with low bone mass. Because body size influences values for bone mineral density that are obtained by dual-energy x-ray absorptiometry, such values are lower in women with small bones than in those with large bones, making the interpretation of a borderline value in a small woman particularly challenging. The optimal interval at which to obtain follow-up measurements of bone mineral

Table 5. Medications Approved by the Food and Drug Administration for the Prevention of Osteoporosis.*

Drug	Dose	Side Effects
Bisphosphonates		Esophagitis, rare occurrence of osteonecrosis of the jaw
Alendronate (Fosamax, Merck)	35 or 70 mg weekly or 5 or 10 mg daily, taken orally†	
Risedronate (Actonel, Procter & Gamble)	35 mg weekly or 5 mg daily, taken orally	
Ibandronate (Boniva, Roche)	150 mg monthly or 2.5 mg daily, taken orally	
Selective estrogen-receptor modulators		
Raloxifene (Evista, Eli Lilly)	60 mg daily, taken orally	Hot flashes, nausea, deep venous thrombosis, stroke, leg cramps
Estrogens‡		Deep venous thrombosis, myocardial infarction, stroke, breast cancer; endometrial hyperplasia and cancer if used without concomitant progestin therapy
Conjugated equine estrogens	0.30–1.25 mg daily, taken orally	
17β-estradiol	0.014–0.1 mg daily, administered either orally or transdermally	

* Specific data on the reduction of fracture risk among patients with osteopenia are available only for alendronate and raloxifene and are limited to reduction of vertebral fractures. These medications are appropriate for only a carefully selected subgroup of women with osteopenia. Data are from Rosen.[32]

† A dose of 35 mg weekly (or 5 mg daily) is the dose approved for prevention of osteoporosis; however, many clinicians use the higher dose approved for treatment, 70 mg weekly (or 10 mg daily), in patients with osteopenia.

‡ On the basis of the risks associated with its use, postmenopausal estrogen therapy is not currently recommended as a first-line option for reducing the risk of osteoporosis. Estrogens are given with concomitant progestin therapy in women with an intact uterus.

density is also controversial. An interval of 2 to 3 years is often reasonable, but some clinicians recommend earlier follow-up (after 1 year), especially in patients with T scores of –2.0 or lower who are not receiving pharmacologic treatment.

GUIDELINES

Clinical practice guidelines from the National Osteoporosis Foundation,[11] the American Association of Clinical Endocrinologists,[50] and the North American Menopause Society[51] all recommend treatment for patients with osteoporosis and those with a fracture, and they advise against treatment for patients with bone mineral density T scores that are higher than –1.0. However, recommendations for the management of osteopenia are inconsistent. For example, whereas the National Osteoporosis Foundation[11] and the American Association of Clinical Endocrinologists[49] suggest at least the consideration of pharmacologic therapy for women with T scores for bone mineral density that are less than –1.5 and additional risk factors, the North American Menopause Society[51] recommends that this intervention be deferred until the T score is lower (–2.0 to –2.5), even with additional risk factors. The development of guidelines by the WHO that combine clinical risk factors with bone mineral density to estimate "absolute" fracture risk (i.e., the likelihood of fracture, expressed as a percentage, over a period of 10 years) may help reduce this controversy and facilitate informed decision-making.[16]

CONCLUSIONS AND RECOMMENDATIONS

The goal of treating low bone mass is to prevent fracture-related morbidity and mortality, an important task, given that the lifetime risk of osteoporotic fracture is 40% for women and 13% for men, even among 50-year-old women and men at average risk.[19] Because osteopenia is so much more common than osteoporosis, the majority of fractures occur in the population of patients with osteopenia,[10,52] yet measurement of bone mineral density alone cannot effectively discriminate between those patients with osteopenia who will have fractures and those who will not. Clinical risk factors should be considered in combination with

measurements of bone mineral density to estimate fracture risk and guide intervention.

The patient described in the vignette is lean and has a family history of hip fracture. She should be counseled on lifestyle measures, including adequate weight-bearing exercise, calcium supplementation to achieve a total intake of 1200 mg per day, and vitamin D supplementation to achieve a serum 25-hydroxyvitamin D concentration above 25 to 30 ng per milliliter (62 to 75 nmol per liter); we would recommend a minimum of 400 to 800 IU of vitamin D per day (more may be needed in some patients). The option of pharmacologic therapy should be discussed with the patient. Since definitive evidence for or against the use of such therapy in patients with osteopenia is lacking, the patient's own valuation of risks and benefits should influence the choice. Unless the patient strongly prefers to take antiresorptive medication or has a T score near the osteoporotic range (e.g., below −2) with several risk factors for fracture, encouragement of lifestyle modifications with reassessment in 2 to 3 years is a reasonable strategy and is our recommendation for the majority of patients with osteopenia.

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REFERENCES

1. Cooper A. A treatise on dislocations and fractures of the joints. London: Churchill, 1842.
2. Lochmuller EM, Burklein D, Kuhn V, et al. Mechanical strength of the thoracolumbar spine in the elderly: prediction from in situ dual-energy X-ray absorptiometry, quantitative computed tomography (QCT), upper and lower limb peripheral QCT, and quantitative ultrasound. Bone 2002;31:77-84.
3. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254-9.
4. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva: World Health Organization, 1994.
5. The frequency of bone disease. In: Bone health and osteoporosis: a report of the Surgeon General. Rockville, MD: Department of Health and Human Services, 2004:68-87.
6. Moynihan R, Heath I, Henry D. Selling sickness: the pharmaceutical industry and disease mongering. BMJ 2002;324:886-91.
7. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72. [Erratum, JAMA 2003;290:197.]
8. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-97.
9. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
10. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacologic intervention to prevent fractures. Arch Intern Med 2004;164:1108-12.
11. Physician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation, 2003. (Accessed May 4, 2007, at www.nof.org/physguide/index.htm.)
12. Raisz LG. Screening for osteoporosis. N Engl J Med 2005;353:164-71.
13. Eddy DM, Johnston CC, Cummings SR, et al. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Osteoporos Int 1998;8:Suppl:S1-S88.
14. De Laet C, Oden A, Johansson H, Johnell O, Jonsson B, Kanis JA. The impact of the use of multiple risk indicators for fracture on case-finding strategies: a mathematical approach. Osteoporos Int 2005;16:313-8.
15. Kanis JA, Black D, Cooper C, et al. A new approach to the development of assessment guidelines for osteoporosis. Osteoporos Int 2002;13:527-36.
16. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005;16:581-9.
17. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180-7.
18. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;35:375-82.
19. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761-7.
20. Kaptoge S, Armbrecht G, Felsenberg D, et al. Whom to treat? The contribution of vertebral x-rays to risk-based algorithms for fracture prediction: results from the European Prospective Osteoporosis Study. Osteoporos Int 2006;17:1369-81.
21. Lewiecki EM, Laster AJ. Clinical applications of vertebral fracture assessment by dual-energy X-ray absorptiometry. J Clin Endocrinol Metab 2006;91:4215-22.
22. Seibel MJ. Biochemical markers of bone turnover. Part I: biochemistry and variability. Clin Biochem Rev 2005;26:97-122.
23. Miller PD, Baran DT, Bilezikian JP, et al. Practical clinical application of biochemical markers of bone turnover: consensus of an expert panel. J Clin Densitom 1999;2:323-42.
24. Hannon R, Eastell R. Preanalytical variability of biochemical markers of bone turnover. Osteoporos Int 2000;11:Suppl 6:S30-S44.
25. Jamal SA, Leiter RE, Bayoumi AM, Bauer DC, Cummings SR. Clinical utility of laboratory testing in women with osteoporosis. Osteoporos Int 2005;16:534-40.
26. Gaugris S, Heaney RP, Boonen S, Kurth H, Bentkover JD, Sen SS. Vitamin D inadequacy among post-menopausal women: a systematic review. QJM 2005;98:667-76.
27. Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev 2002;23:552-9.
28. Papadimitropoulos E, Wells G, Shea

B, et al. Meta-analyses of therapies for postmenopausal osreoporosis. VIII. Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23:560-9.
29. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669-83. [Erratum, N Engl J Med 2006;354:11-2.]
30. Martyn-St James M, Carroll S. High-intensity resistance training and postmenopausal bone loss: a meta-analysis. Osteoporos Int 2006;17:1225-40.
31. Palombaro KM. Effects of walking-only interventions on bone mineral density at various skeletal sites: a meta-analysis. J Geriatr Phys Ther 2005;28:102-7.
32. Rosen CJ. Postmenopausal osteoporosis. N Engl J Med 2005;353:595-603.
33. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 2002;23:508-16.
34. Cranney A, Tugwell P, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23:517-23.
35. Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. Endocr Rev 2002;23:524-8.
36. Wells G, Tugwell P, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23:529-39.
37. Kanis JA, Johnell O, Black DM, et al. Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: a reanalysis of the Multiple Outcomes of Raloxifene Evaluation trial. Bone 2003;33:293-300.
38. Quandt SA, Thompson DE, Schneider DL, Nevitt MC, Black DM. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of -1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. Mayo Clin Proc 2005;80:343-9.
39. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82.
40. Cauley JA, Robbins J, Chen Z, et al. Effect of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003;290:1729-38.
41. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 2001;12:989-95.
42. Schousboe JT, Nyman JA, Kane RL, Ensrud KE. Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women. Ann Intern Med 2005;142:734-41.
43. Miller PD, Zapalowski C, Kulak CA, Bilezikian JP. Bone densitometry: the best way to detect osteoporosis and to monitor therapy. J Clin Endocrinol Metab 1999;84:1867-71.
44. Kanis JA, Melton LJ III, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994;9:1137-41.
45. Blake GM, Chinn DJ, Steel SA, et al. A list of device-specific thresholds for the clinical interpretation of peripheral x-ray absorptiometry examinations. Osteoporos Int 2005;16:2149-56.
46. Melton LJ III. The prevalence of osteoporosis: gender and racial comparison. Calcif Tissue Int 2001;69:179-81.
47. Wilkins CH, Goldfeder JS. Osteoporosis screening is unjustifiably low in older African-American women. J Natl Med Assoc 2004;96:461-7.
48. Sinnott B, Kukreja SC, Barengolts EI. Utility of screening tools for the prediction of low bone mass in African American men. Osteoporos Int 2006;17:684-92.
49. Orces CH, Casas C, Lee S, Garcia-Cavazos R, White W. Determinants of osteoporosis prevention in low-income Mexican-American women. South Med J 2003;96:458-64.
50. Hodgson SF, Watts NB, Bilezikian JP, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocr Pract 2003;9:544-64. [Erratum, Endocr Pract 2004;10:90.]
51. North American Menopause Society. Management of osteoporosis in postmenopausal women: 2006 position statement of the North American Menopause Society. Menopause 2006;13:340-67.
52. Pasco JA, Seeman E, Henry MJ, Merriman EN, Nicholson GC, Kotowicz MA. The population burden of fractures originates in women with osteopenia, not osteoporosis. Osteoporos Int 2006;17:1404-9.