Osteoporosis Guideline Team

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Osteoporosis: Prevention and Treatment

Patient population: Postmenopausal women and persons at risk for secondary osteoporosis related to long-term glucocorticoid use, organ transplant, or other medical conditions.

Objective: Decrease osteoporotic fractures and their associated morbidity and mortality.

Key Points

Definitions

Bone mineral density [BMD] correlates with skeletal strength and fracture risk.

Dual-energy X-ray absorptiometry [DXA] measures BMD.

A DXA *T-score* is the number of standard deviations from mean BMD in young adults.

Osteoporosis is defined as a DXA T-score ≤ -2.5, *osteopenia* as > -2.5 but < -1.0 (Table 1).

General Clinical Relevance

Fractures related to osteoporosis are common and have high morbidity *[C]*.

Glucocorticoids can cause significant bone loss, particularly during the first 6-12 months of use *[B]*.

Prevention

Across life span: appropriate calcium & vitamin D (Table 9) and weight bearing exercise *[ID]*.

Risk Assessment and Diagnosis

Assess all adults, men and women, for clinical risk factors for osteoporotic fracture (Tables 2 & 3) *[IC]*:

- Postmenopausal woman with one or more of the following:
  - Age ≥ 65 years   – Current smoking
  - Low body weight (BMI < 20)   – Frailty (e.g., unable to rise from chair unassisted)
  - Personal history of fracture without substantial trauma
  - Hip wrist, or spine fracture without substantial trauma in 1st degree relative ≥ 50
- Chronic glucocorticoid use (prednisone ≥ 5 mg daily, or equivalent, for ≥ 3 months).
- Organ transplant or pending transplant.   • Other associated medical conditions (Table 2)
- Risk for falling (Table 4).   and medications (Table 3).

Order DXA *[IA]* based on clinical risk factors & potential impact of results on management (Table 5).

For women under 65, FRAX (http://www.shef.ac.uk/FRAX/) can be used to assess need for screening DXA. DXA is indicated for women with 10-year total fracture risk of 9.3% (equivalent to that of a healthy 65 year-old woman). In this setting, FRAX can be used without entering BMD data.

Evaluate appropriately and refer, when indicated, for secondary causes of osteoporosis (Table 6) *[IID]*.

Treatment

For treatment-naive women, FRAX (http://www.shef.ac.uk/FRAX/) can be used to assess need for treatment. Begin medical therapy for 10-year fracture risks of >3% at hip or >20% total fracture risk. For other patients, based on T-score & clinical risk factors (Tables 2, 3 & 5), begin medical therapy for:

- Prior osteoporosis-related fracture, or T-score < -2.5 *[IA]*.
- T-score ≤ -1 and (a) glucocorticoid use or (b) pending or post-transplant, especially if on steroids or (c) postmenopausal woman at high risk *[IA]*.
- T-score between -2 and -2.5 in postmenopausal woman *[IA]* and patients with appropriate risk factors.

When starting glucocorticoids, consider medical therapy to prevent or treat osteoporosis *[IIA]*.

Base medical therapy (Tables 7 & 9) on clinical benefits and potential risks *[I]*:

- In post-menopausal women with osteoporosis:
  - Alendronate, denosumab, estrogen, risedronate, & zoledronic acid reduce hip and vertebral fracture risk *[A]*.
  - Ibandronate, raloxifene, teriparatide, and calcitonin reduce vertebral fracture risk *[IA]*.
- In men with osteoporosis, alendronate reduces vertebral fracture risk *[A]* (probably class effect *[D]*).
- If on a glucocorticoid, use bisphosphonates (oral or IV) *[A]*. For alternative treatments, consider teriparatide or denosumab *[A]*.

Follow-up

Repeat DXA based on patient's situation (Tables 5 & 8) *[IC-D]*. Consider not repeating DXA on patients with moderate bone loss who are fracture-free on medical therapy *[IIC]*.

For most persons, ≥ 2 years between DXAs provides the most meaningful information *[B]*.

Early in glucocorticoid use and/or after transplantation consider repeating DXA in 6-12 months *[IB]*.

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* **Strength of recommendation:**
  I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.
Levels of evidence reflect the best available literature in support of an intervention or test:
  A=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

Table 1. World Health Organization Definitions

Classification	DXA T-score*
Normal	$\geq$ -1.0
Osteopenia	> -2.5 and < -1.0
Osteoporosis	$\leq$ -2.5

*SD from young adult white women

Table 2. Clinical Risk Categories for Osteoporosis and Osteoporotic Fractures

Extremely High Risk	High Risk
Prior osteoporotic fracture[a] (fracture without significant trauma) Glucocorticosteroid use[b] (prednisone $\geq$ 7.5 mg/d or equivalent for $\geq$ 6 months) Solid organ transplant[c] (pre or post, especially in first 2-3 yrs)	Glucocorticosteroid use[b] (prednisone $\geq$ 5mg/ day or equivalent, for $\geq$ 3 months) Woman age > 65 yrs or men age > 70 yrs Postmenopausal woman or older man with one or more of: • Personal history of low impact fracture • Family history of fracture hip, wrist, or spine (first-degree relative age $\geq$ 50 yrs) • Currently smoking • Rheumatoid arthritis • Body Mass Index [BMI] < 20 • Multiple risk factors for falling (see Table 4)

Moderate Risk

Hormonal conditions
- Hypogonadism
- Late menarche (age > 15 yrs)
- Early menopause (age < 45 yrs)
- Premenopausal amenorrhea, (e.g., anorexia nervosa, exercise, or hyperprolactinemia but not polycystic ovary syndrome or pregnancy)
- Cushing's syndrome
- Hyperparathyroidism (primary or secondary)
- Thyrotoxicosis

Gastrointestinal and nutritional factors
- Gastrectomy
- Low gastric acid (e.g., atrophic gastritis, proton pump inhibitors, H2 –blockers)
- Impaired absorption
  - Celiac disease
  - Bariatric surgery
  - Inflammatory bowel disease (Crohn's disease more than ulcerative colitis)
  - Pancreatic insufficiency
- Heavy alcohol use

Medications (see Table 3)
Family history of osteoporosis
Other significant associations
- Severe liver disease
- Chronic kidney disease
- Type 1 diabetes mellitus
- Multiple myeloma
- Hemochromatosis
- Long-term immobilization
- Prior smoking

Other possible associations
- Addison's disease
- Amyloidosis
- Thalassemia (major > minor)
- Multiple sclerosis
- Nephrolithiasis
- Sarcoidosis
- Depression

[a] Prior fracture is more predictive of future fracture than is BMD.
[b] Glucocorticoids produce the greatest bone loss in the initial 6-12 months of use, average 4%-5%.
[c] Bone loss can be as much as 10% in the first year after transplant.

Table 3. Medications with Risk for Bone Loss or Fracture

Definite risk	Possible risk
Immunosuppressants • Glucorticoids (systemic >> inhaled[a], intranasal, topical, others) • Cyclosporine [Gengraf®, Neoral®, Sandimmune®] • Tacrolimus [Prograf®] • Mycophenolate mofetil [CellCept®] Hormonal and antihormonal agents • Medroxyprogesterone acetate [Depo-Provera®][b] • Tamoxifen, before menopause • Aromatase inhibitors (anastrozole/Arimidex®, letrozole/Femara®) • GnRH analogs (leuprolide/Lupron®, goserelin/Zoladex®) • Thiazolidinediones (pioglitazone/Actos®, rosiglitazone/Avandia®) Miscellaneous • Anticonvulsants (phenytoin or phenobarbital > carbamazepine or valproic acid)[b] • Heparins (unfractionated > low molecular weight)	Miscellaneous • Lithium • Selective serotonin reuptake inhibitors • Antipsychotics (may cause hyperprolactinemia) • Excessive supplemental fluoride • Proton pump inhibitors • Topiramate

>, greater than; >>, much greater than.
[a] Inhaled beclomethasone (>1600 µg gaily) is associated with risk for bone loss and fracture (inhaler doses range 40-100 µg per spray).
[b] BMD loss related to depot medroxyprogesterone acetate appears to be reversible or nearly reversible. There are minimal data on reversibility of associated fracture risk.

Table 4. Risk Factors for Falling

Decreased leg or arm muscle strength	Impaired gait, balance, or transfer skills
Diminished vision	Impaired range of motion
Environmental hazards for falls	Increasing age
Frailty (unable to rise from chair unassisted)	Low physical function
History of falls	Postural hypotension
Impaired cognition	Use of any psychotropic medication

Table 5. Screening & Management Based on Risk for Osteoporotic Fractures*

Screening and Management using FRAX
- For women under age 65, FRAX (http://www.shef.ac.uk/FRAX/) can be used to assess need for screening DXA. DXA is indicated for women with 10-year total fracture risk of 9.3% (equivalent to that of a healthy 65 year-old woman). In this setting, FRAX can be used without entering BMD data.
- For treatment-naive women, consider using the FRAX to assess need for treatment. 10-fracture risks of >3% at hip or >20% total fracture risk are considered reasonable indications for treatment.

Clinical Risk (Include factors in Tables 2 & 3 not addressed by FRAX)	Order first DXA?[a]	Management Based on DXA[b]			Reassess Clinical Risk Factors	Repeat DXA?[a] See table 8
		T < -2	T -2 to -1	T > -1		
Extremely High	Yes	Treat	Treat	Consider preventive Rx [c]	1 year	Consider in 1 year
High	Yes	Treat	Consider treatment	Life style [d]	1 year	If prior T > -1, wait at least 3-5 years
Moderate	Consider	Consider treatment	Life style [d]	Life style [d]	1-2 years	If prior T ≤ -1, wait at least 2 years

* DXA $100-$488 as of 10/11. Lower price is reimbursement accepted from Medicare. Higher price is that charged by UMHS. Payment accepted from most commercial insurance is ~50% of UMHS charge.
[a] Order DXA only if results will affect patient management: not already receiving full therapy; not tolerating current therapy; possible candidate for zoledronic acid, teriparatide, or denosumab; fractures occurring despite treatment; considering discontinuation of therapy; etc.
[b] Lowest T-score from femoral neck, total hip, or combination of lumbar vertebra. Wards triangle is not predictive of fracture risk [D].
[c] If patient has had fracture without significant trauma, consider other causes of bone abnormality, e.g., malignancy.
[d] Lifestyle = ensure appropriate intake of calcium and vitamin D, along with weight bearing exercise.

Table 6. Evaluation for Secondary Causes of Osteoporosis and Osteopenia *[D]*

All patients: consider calcium, alkaline phosphatase, renal function, liver function tests, TSH, 25-hydroxy-vitamin D. [Comprehensive metabolic panel $20-160, TSH $47-212, 25-hydroxy-vitamin D $53-61]

Men: consider testosterone [Free: $47-158, Total: $47-212] (1/3 of older men with osteoporosis have hypogonadism *[C]*)

Premenopausal amenorrhea not due to pregnancy or polycystic ovary syndrome: estradiol [$50-164], FSH [$81-136] *(hypogonadism)*

Based on clinical situation:
- 24-hour urinary calcium [$10-44], or spot urinary calcium/creatinine ratio *(abnormal calcium excretion)*
- [1,25-dihydroxy-vitamin D is rarely helpful in setting of normal renal function.]
- Intact-PTH [$75-246] with calcium [$10-44] *(hyperparathyroidism, primary or secondary)*
- 24-hour urine free cortisol [$31-130] or 1 mg dexamethasone suppression [$8] *(Cushing's syndrome)*
- Evaluation for occult malignancy, such as multiple myeloma, bony metastases, etc.

Note: Lower price is reimbursement accepted from Medicare. Higher price is that charged by UMHS. Payment accepted from most commercial insurance is ~50% of UMHS charge. Cost information as of 9/09.

Table 7. Selection of Therapy Based on Patient and Medication Characteristics

Prevention or treatment (many, if not most, patients require supplements):
  Calcium, typically carbonate or citrate, Vitamin D.

First line for most: Bisphosphonate, oral. (Intravenous if not able to take oral.)

Woman not able to use bisphosphonate: teriparatide, denosumab, estrogen, or raloxifene

Hypogonadal man: Testosterone.

Unable to use other agents: Nasal calcitonin.

Acute osteoporotic fracture: Two to four week trial of nasal calcitonin may reduce pain in some patients.

Fracture or other evidence of worsening and severe osteoporosis despite other therapy:
  Teriparatide or denosumab.

Table 8. Considerations for Additional DXA Testing

Clinical risk factors (Tables 2 & 3).
  Clinical changes since previous risk assessment and testing, especially:
  - New fracture.
  - Glucocorticoid therapy.
  - Solid organ transplant.

Patient considerations.
  Clinical context, e.g., co-morbid conditions, life expectancy.
  Treatment options.
  Acceptance of and adherence to recommended therapy.
  Possibility that additional DXA results will change patient behavior.

Bone mineral density [BMD] data.
  Prior DXA results:
  - Baseline degree of bone loss.
  - Improvement or deterioration across time.
  - Relative rate of change.
  Likelihood that new DXA data will change management.

Management factors.
  Adequate calcium and vitamin D intake.
  Prior types and duration of therapy.
  Interval changes in treatment.

Table 9. Pharmacologic Therapy for Osteoporosis Treatment and Prevention

AGENT	DOSE	COST/30 DAYS[*] Generic	Trade	OTHER CONSIDERATIONS
Prevention				
Calcium (typically as carbonate or citrate)	Total daily intake 1000-1500 mg of elemental calcium	$4-10		• Constipation is more common with calcium carbonate • Calcium citrate is more expensive, but probably better absorbed in patients with low stomach acidity (e.g., PPI use) • Nephrolithiasis is not a contraindication
Vitamin D	Total daily intake 800-1000 IU	$4		• 10-30 min sun exposure to arms & face 2-3x/week during summer months • For high doses or calcitriol consider specialist consultation
Treatment, listed in decreasing order of approximate quality and quantity of data supporting efficacy				
Bisphosphonates, oral				• Take 30-60 min before 1st food of day with 8 oz water; stand/sit upright for 30-60 min
Alendronate (Fosamax®)	70 mg po weekly	$11	$88	• Mild GI effects excess 0-5% cf. placebo; severe GI effects are rare
Ibandronate (Boniva®)	150 mg po monthly	NA	$112	• Reflux w/o esophagitis is relative but not absolute contraindication
Risedronate (Actonel®)	35 mg po weekly,	NA	$104	• Renally excreted, avoid if creatinine clearance <30-35.
	150 mg po monthly		$112	• Effects on fetal development are not known. Discuss potential fetal risks if considering for women of child-bearing age
Bisphosphonates, parenteral				
Ibandronate (Boniva®)	3 mg IV Q 3 mo		$454	• Risk of osteonecrosis of jaw is less than 1 in 100,000 for oral bisphosphonates.
Zoledronic acid (Reclast®)	5 mg IV yearly		$1159	• For zoledronic acid – monitor for increased creatinine and hypocalcemia
Teriparatide (rDNA origin) (FORTEO®)	20 mcg SQ daily	NA	$938	• Consider specialist consultation
Denosumab (Prolia®)	60 mg SQ q 6months		$891	• Administered in clinical settings • Consider specialist consultations • Denosumab is a monoclonal antibody • Small increase in skin infections have been reported
Raloxifene (Evista®)	60 mg po daily	NA	$117	• Increased deep venous thrombosis and pulmonary embolism risk - approximately same as estrogen therapy [A] • Hot flash incidence 3-6% greater than placebo • Not indicated for men or for premenopausal women
Hormone therapy, Postmenopause **Estrogens**				
Estradiol (Estrace®)	1 mg po daily	$6	$61	
Estropipate (Ogen®)	0.625 mg po daily	$5	$30	
Conjugated estrogens (Premarin®)	0.625 mg po daily	NA	$52	• The relative risks and benefits of postmenopausal estrogen therapy should be reviewed with patients before starting treatment.
Transdermal estradiol (various)	0.05 mg/d 1-2x/wk	$31	$58	• Women with uterus in place will need both estrogen and progestin therapy
Combinations (dose ranges of estrogen and progestin)				• Level A evidence is only with conjugated estrogens, but this is likely a class effect [D]
Prempro™	0.3/1.5 mg daily to 0.625/2.5 mg daily	NA	$62	
Calcitonin Nasal Spray (Miacalcin®, Fortical®)	200 IU daily, alternate nostrils	$75	$93-121	• Rhinitis 5% excess compared to placebo [A] • Caution in renal failure • Reduces pain of acute fracture [A]

* Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + $3 for generics on 30-day supply, Amerisource Bergen item catalog, 7/10, and Michigan Department of Community Health M.A.C. Manager, 7/10.

Clinical Background

Clinical Problem and Management Issues

Osteoporosis and associated fractures are significant public health issues that are expected to become more important as the population of the United States ages. Fortunately, effective strategies for prevention and treatment are available.

Incidence and risks. Approximately 10 million Americans have osteoporosis and an additional 34 million have low bone mass. Gender, age, and race are important risk factors for osteoporotic fractures. Of the 10 million people with osteoporosis, 8 million are women. At least 55% of American postmenopausal woman have decreased bone density at the hip. In women over the age of 80, the prevalence of osteoporosis is 44%, 10 times greater than women in their 50s. The lifetime probability of a hip fracture for an average white woman is 14%; the risk for a white man or a black woman or man is roughly 5-7%.

Certain medications (particularly glucocorticoids) and various medical conditions (e.g., renal failure, hypogonadism, and alcoholism) are important secondary causes of osteoporosis. Among women with osteoporosis, between 30% and 60% have a secondary cause. Solid organ transplant is another major risk factor for osteoporotic fractures. Younger women (ages 25-44) with kidney transplants have an 18-fold increase in fractures, with the risk increasing to 34-fold among older transplant recipients.

Morbidity, mortality, and cost. In its 2004 report, the Surgeon General's office estimated that 1.5 million osteoporotic fractures occur annually. An osteoporotic hip fracture can result in up to 10-20% excess mortality within 1 year. At least one in two of all women with hip fractures spends some time in a nursing home; one in five requires long-term nursing care. Osteoporotic fractures can also result in chronic pain, disability, deformity, and/or depression. In a survey of women, all at least 75 years old (n=194, mean age 83), 80% preferred death over a bad hip fracture that caused substantial, permanent loss of independence and admission to nursing home.

Direct medical costs for the treatment of osteoporotic fractures in persons greater than age 45 are at estimated to be least $15 billion annually (in 2002 dollars). This represents roughly 7% of health care costs for that group and 14% of nursing home days. Indirect costs (e.g., lost time and earnings for patients and family members) are significant, but difficult to estimate.

Rationale for Recommendations

Definitions

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue predisposing to an increased risk of fracture. The clinical diagnosis combines evidence of fragility fractures with measurement of bone mineral density [BMD]. BMD correlates with bone strength, skeletal load-bearing capacity, and fracture risk. The widely used World Health Organization [WHO] definitions compare patient BMD to norms expressed as *T-scores,* the number of standard deviations [SDs] from the mean BMD in young white adult women (Table 1). *Osteoporosis* is defined as a T-score at any site of -2.5 or lower, while *osteopenia* is defined as a T-score between -1 and -2.5. The presence of a fracture in the absence of significant trauma is strong evidence of osteoporosis, but the diagnosis should generally be confirmed by BMD measurement. BMD in the osteoporotic range is a good predictor of increased fracture risk. In contrast, osteopenia is less helpful, as it encompasses a broader range of bone mineral densities.

In younger patients, BMD results are given as Z-scores, the number of standard deviations from the mean BMD for women of the same age as the patient. Although osteoporosis cannot be 'officially' diagnosed by Z-scores, markedly low Z-scores (e.g., <-2.5) may be useful in assessing fracture risk in younger patients.

Similarly, no standard diagnostic criteria for osteoporosis exists for men. Most authorities use the WHO criterion: a T-score of $\leq$ -2.5 relative to normal young men in conjunction with clinical risk factors and presentation. Although men have much higher baseline BMD than women, they seem to have similar fracture risk for a given BMD.

Etiology and Pathophysiology

Normal bone loss. Bone remodeling is an ongoing, cyclic process of bone formation and resorption at the cellular level. *Osteoclasts* adhere to bone and remove it, while *osteoblasts* secrete osteoid and help build bone. Any imbalance in these two processes produces net bone loss or gain. Antiresorptive medications, such as bisphosphonates, interfere with osteoclast action, and are the mainstay of osteoporosis therapy. Anabolic (bone building) therapy is currently limited to recombinant parathyroid hormone.

Bone has trabecular and cortical components. Trabecular bone predominates in vertebrae and the proximal femur, whereas cortical bone is prominent in the long bone shafts.

Trabecular remodeling occurs at a rate of approximately 25% per year while the cortical rate is approximately 3% per year. Thus, changes in bone mineral density occur more quickly and have greater clinical implications in trabecular bone, which is consistent with the prevalence of vertebral and femoral fractures in patients with osteoporosis.

Glucocorticoid related bone loss. The etiology of glucocorticoid-induced osteoporosis and associated fractures is not fully understood, but is multifactorial and different from postmenopausal osteoporosis. Bone resorption is increased, possibly due to stimulation of osteoclast differentiation. Meanwhile, bone formation is reduced, due to inhibition of osteoblasts. Calcium balance becomes negative, owing to a decrease in gastrointestinal absorption and an increase in urinary loss. Also, glucocorticoids inhibit production of sex steroid hormones, which affects the bone remodeling cycle. Glucocorticoid-induced myopathy as well as inactivity caused by underlying illness may contribute both to a decline in BMD by reduction in skeletal loading and to an increase in fracture risk related to greater fall risk.

Bone loss is most rapid during the first 6 to 12 months of glucocorticoid therapy, and, as in early menopause, trabecular bone is affected more than cortical. Bone loss in the first year after transplant has been reported to be as high as 10%. In chronic glucocorticoid use, fracture risk is higher for a given BMD than in postmenopausal osteoporosis, suggesting that there are glucocorticoid-induced qualitative bone defects. A large retrospective cohort study strongly suggests that glucocorticoid doses as low as 2.5 mg daily may increase fracture risk.

Clinical Risk Factors

BMD, by itself, is an excellent predictor of fracture risk, at least as good as cholesterol as a predictor of heart disease, and blood pressure as a predictor of stroke. However, multiple clinical factors, including family history, medical conditions, and medications, are also important in the assessment of patients at risk for low bone density and osteoporotic fractures (Tables 2 & 3). Patients at highest risk include those with prior osteoporotic fractures, long-term glucocorticoid use, and/or solid organ failure or transplant. Usually, an osteoporotic fracture is closely involved with a fall, and risk of falling is an independent risk for osteoporotic fracture (Table 4).

Assessment of clinical factors and fall risk is useful in identifying patients who might benefit from further evaluation. Several models have been proposed to stratify osteoporotic risk. One well-regarded model, FRAX, is based on WHO data on fracture risk, and is available online (http://www.shef.ac.uk/FRAX/)

Age. Skeletal mass is maximal in the third decade of life and depends primarily on diet (especially calcium and vitamin D), physical activity, and genetics. Bone density in later life depends on both the peak mass achieved in youth and on the subsequent rate of bone loss.

Gender. During the first few years after menopause, women typically have a rapid loss of bone, as much as 5% per year in trabecular bone and 2-3% per year in cortical bone. This early postmenopausal loss is primarily due to increased osteoclast activity. Later, a decline in osteoblast activity predominates and the rate of loss slows to 1-2% or less per year.

Risk factors for osteoporosis and related fracture have been most studied in white women. Little data are available in men, but risk factors appear to be similar to those for women. As many as a third of older men with osteoporosis have low testosterone levels. For unclear reasons, men with hip fractures have a higher mortality than women. One possible explanation is that men fracture their hips about 10 years later than women. Another theory is that men who fracture a hip tend to be sicker, putting them at increased risk for post-fracture complications.

Ethnicity. Bone strength and risk factors for fracture differ by race.

HIP FRACTURE	White		Black	
	♀	♂	♀	♂
Incidence, per yr per 1000	10.1	4.3	4.1	3.1
Risk %, between ages of 65-90	16.5	5.3	5.5	2.6

In community-dwelling white women age 65 years and older, osteoporotic fracture is significantly correlated with: previous fracture of any type after age 50; maternal history of hip fracture; long-acting benzodiazepine or anticonvulsant drug use; previous hyperthyroidism; excessive caffeine intake; standing four hours or less per day; difficulty rising from a chair (frailty); poor vision; and resting tachycardia. Risk factors for hip fracture in black women age 45 years and older include: lowest quintile in body mass index [BMI]; use of aids in walking; and history of stroke.

Falls. Women with low BMD and multiple risk factors for falling are 27 times more likely to sustain a fracture than are women with normal BMD and no more than two of these risk factors.

Among the elderly, one-third of community dwelling and one-half of nursing home residents fall each year. Among such falls, 2% result in hip fracture and up to 5% result in other fracture. Low femoral BMD and low BMI are risk factors for fall-related injury. Major injuries are more likely in a fall from an upright position or a fall laterally with direct impact to the hip.

Glucocorticoids. Risk factors for glucocorticoid-induced osteoporosis and associated fractures, although not studied in detail, probably include low BMD at start of glucocorticoid therapy, the underlying disease that requires

glucocorticoid therapy, postmenopausal state, older age, and previous fracture.

Bone loss associated with glucocorticoid therapy occurs in a dose dependent manner, increasing with greater duration of use and/or magnitude of dose. The threshold for significant risk seems to be oral prednisone 7.5 mg or more (or equivalent) for 6 months or longer. Lower doses for extended periods and even prolonged use of inhaled steroids may cause abnormal bone loss.

Organ failure and transplantation. Patients with organ failure, particularly liver and kidney, are at significant risk for osteoporosis and fracture. The risk is further increased after transplantation, particularly within the first 2 to 3 years. This is most likely due to greater steroid use, although other medications, such as cyclosporine and tacrolimus, may be factors.

Prevention of Osteoporosis and Related Fractures

General prevention. Encourage all patients to eat a balanced diet that includes adequate calcium and vitamin D (using supplements only when necessary), engage in regular physical activity, avoid heavy alcohol consumption, and refrain from smoking. Specific recommendations for calcium and vitamin D intake are discussed below (see Pharmacologic Therapy).

Glucocorticoid-induced osteoporosis prevention. The various guidelines for osteoporosis prevention in relation to glucocorticoid use differ in specifics, but agree in general principles. Minimize exposure to glucocorticoid by using the lowest effective daily dose for the shortest period. When possible, use inhaled or topical rather than oral preparations, although high dose inhaled steroids have also been shown to cause bone loss. Every other day dosing has not been shown superior to daily dosing with respect to bone loss. Consider preventive therapy for any patient taking glucocorticoids, regardless of dose or duration:

For patients taking lower doses for shorter durations (e.g., prednisone less than 5 mg daily for fewer than 3 months), who have no history of bone loss, ensure adequate calcium and vitamin D supplementation when necessary. For those with pre-existing bone loss, consider bisphosphonate therapy.

For higher doses of glucocorticoids (prednisone more than 7.5 mg daily for longer than 6 months) oral bisphosphonates remain the most cost-effective therapy, as they have been shown to prevent glucocorticoid-related bone loss at both the lumbar spine and femoral neck, and to reduce the risk of vertebral fractures. However, other agents such as zoledronic acid and recombinant PTH are also FDA approved for prevention of glucocorticoid-induced bone loss.

Diagnostic Testing

DXA. Dual energy X-ray absorptiometry [DXA] is the test of choice for measuring BMD. The technique compares soft tissue and bone penetration of two different X-ray sources, then 'subtracts' soft tissue, leaving an estimate of skeletal BMD. A study typically takes less than 10 minutes, and radiation exposure is about 3-4 mrem/site. By comparison, background radiation is about 300 mrem/year.

Although various skeletal sites can be assessed by DXA, BMD of the nondominant hip is the best predictor of hip fracture and is an excellent predictor of vertebral or wrist fracture. Loss of vertebral bone is accelerated early in menopause and early in glucocorticoid use. Spine BMD measurements may be particularly helpful in these settings.

BMD measurement by DXA may be spuriously elevated by a number of factors. Vertebral compression fractures typically result in a 'smaller' vertebral body with no change in the total amount of calcium, and thus produce an apparent increase in BMD. Vertebral osteophytes, degenerative joint disease, and aortic calcifications can also falsely raise BMD measurements. Hip measurements tend to have fewer artifacts.

Medicare and many other major insurers cover DXA for patients at risk, including all women age 65 years or greater and patients with primary hyperparathyroidism, vertebral abnormalities, or chronic glucocorticoid use. Follow-up studies are covered, usually at no less than two-year intervals, though more frequently when indicated (e.g., chronic glucocorticoid use). Medicare will also cover a follow-up BMD test every two years (> 23 months since last BMD test) to monitor response in those patients undergoing FDA-approved treatments of osteoporosis.

Initial screening with DXA is addressed in Table 5. Women age 65 and above, and women under the age of 65 with a total 10-year fracture risk equivalent to a 65-year old (9/3%) should have a screening DXA. FRAX can be used without DXA data to assess fracture risk in this younger group. Recommendations for initial screening based on a larger group of clinical risk factors is outlined in Tables 2, 3, and 4. (Repeat DXA screening is addressed as part of the discussion of "Follow Up," after the discussion of treatment.)

When possible, use the L1-L4 value to diagnose osteoporosis at the spine. If anatomic abnormalities are present, use any combination of two or three vertebrae (e.g. L2-L4). Guidelines suggest *not* making a diagnosis of osteoporosis based on the T-score of one vertebral body.

For diagnosing osteoporosis of the hip, the femoral neck or total hip are the preferred sites.

Other diagnostic and monitoring modalities. Other testing modalities are available, but have limitations in routine testing.

Quantitative calcaneal ultrasound devices are both portable and inexpensive, and are often used in informal osteoporosis screening programs, such as health fairs. However, meta-analysis suggests limited value for ultrasound screening. For example, a positive study in an otherwise healthy 65 year-old woman raises the likelihood of DXA confirmed osteoporosis from a population-based pre-test estimate of 22% only to 34%. Conversely, a negative study reduces the likelihood of osteoporosis from 22% to 10%. T-scores provided by ultrasound are not equivalent to DXA T-scores, and should therefore not be used for diagnostic purposes. Instead, patients with abnormally low ultrasound T-scores should be evaluated by DXA for more definitive diagnosis.

Biochemical markers of bone resorption are used in research and may be used clinically to assess the effectiveness of antiresorptive therapy. In the latter setting, a decrease in these markers to premenopausal levels usually occurs after two to three months of therapy. Some data suggest that elevated levels of bone resorption makers in older women are an independent risk factor for fractures. However, bone markers are not a reliable predictor of BMD, and are not a substitute for DXA in women at risk. Generally, their use in the *diagnosis* of osteoporosis is not recommended.

Evaluation of Secondary Causes

Although most cases of osteoporosis are idiopathic, there are several secondary causes (Tables 2 & 3). Many of these are treatable (e.g., hypogonadism, hyperparathyroidism, malabsorption) or important to diagnose (e.g., renal failure, multiple myeloma), thus a focused evaluation usually is indicated (Table 6).

Vitamin D inadequacy (< 30 ng/mL) is increasingly recognized as contributing to bone loss. More than 50% of postmenopausal women being treated for osteoporosis are vitamin D deficient. However, vitamin D inadequacy is not limited to patients with osteoporosis. Nearly 50% of young women probably have insufficient vitamin D, particularly at the end of winter. A study of Boston health professionals demonstrated that 32% had low vitamin D levels. Based on these findings, consider assessment of vitamin D levels, or empiric vitamin D supplementation (see below), in patients with decreased bone density.

Consider secondary hyperparathyroidism (normal or low calcium with elevated parathyroid hormone) in patients with renal insufficiency or when inadequate intake or absorption of calcium and/or vitamin D is suspected. Calcium hyperexcretion may lead to negative calcium balance, and can often be treated with thiazide diuretics. Subclinical hypercortisolism is not traditionally considered a risk factor for bone loss, but a recent prospective study suggests it may be more common than previously suspected.

Measure serum testosterone in men with osteoporosis if results will affect management. Approximately one-third of older men who have osteoporosis without other secondary cause have low serum testosterone.

Whom to Treat

Base treatment decisions on a patient's future risk for bone loss and fracture as well as on their quantitative bone density.

- Pre-existing osteoporotic fracture: may be treated on that basis alone, although a DXA may be useful in some situations, such as when trying to differentiate between an osteoporotic fracture and a pathologic fracture due to metastatic disease.

- Treatment-naïve women: the FRAX tool (http://www.shef.ac.uk/FRAX/) can be used. A ten-year fracture risk of >3% at hip or >20% total fracture risk is generally considered an indication to begin pharmacologic therapy.

- Other patients: treatment decisions should be based on a combination of DXA T-score and other clinical risk factors. For example, a 65 year-old woman with a T-score of -1.5 would not typically require pharmacologic therapy. However, the same woman on chronic glucocorticoids would benefit from treatment. Table 5 provides guidelines for patient management based on both BMD and clinical risk factors.

Non-Pharmacologic Strategies

Exercise. Observational data and clinical trials indicate that weight-bearing activities, such as aerobics, walking, and resistance training are effective at increasing spine BMD. Most of these studies are of limited quality, primarily due to the difficulty of blinding patients. Exercise has not been shown to reduce the risk of osteoporotic fractures.

Fall prevention measures. Prevention of falls requires attention to the numerous risk factors (Table 4), including medications, gait, vision, and environmental hazards (e.g., poor lighting, area rugs, and lack of handrails in bathrooms). In addition to addressing possible medical causes of falls, consider the potential value of an occupational therapy assessment to reduce fall risk.

Hip protectors. Hip protectors are anatomically designed plastic shields or pads worn in side pockets of special underwear. In spite of multiple randomized trials, the benefit of hip protectors remains unclear. Hip protectors are often difficult to put on, and uncomfortable to wear; therefore compliance may play a role in reducing their potential effectiveness.

Main Pharmacologic Therapies

Medications commonly used to prevent and treat osteoporosis are summarized in Table 7. Table 9 presents dosing, costs, and some common considerations.

In assessing the effectiveness of different therapies for osteoporosis, both clinical (fractures) and radiologic (changes in BMD) endpoints have been used. While clinical endpoints are preferable, they are not always practical. For example, the studies that demonstrated the effectiveness of bisphosphonates and estrogen over placebo in reducing hip fractures required over 10,000 patients. Thus, many studies rely on changes in BMD as a surrogate marker. Although low BMD is an excellent predictor of fracture risk in postmenopausal women, increases in BMD have shown an inconsistent relationship to fracture.

Each of the available classes of antiresorptive agents (bisphosphonates, denosumab, raloxifene, estrogens, and calcitonin) as well as the only available anabolic agent (recombinant parathyroid hormone) reduces vertebral fracture rates in postmenopausal women, independent of effects on BMD. Most of these medications also show reduced fracture risk at *combined* non-vertebral sites. While this term includes hip fractures, it also includes other sites such as ribs and wrist. At the present time, the only medications with clinical data supporting reduction of hip fractures are alendronate, risedronate, zoledronic acid, denosumab and estrogen.

Although reduced BMD is correlated with fracture risk in postmenopausal women, no definite relationship has yet been demonstrated in glucocorticoid-induced osteoporosis. Nonetheless, most studies of therapy for glucocorticoid-induced osteoporosis have used change in BMD as the primary endpoint although some have been sufficiently powered to demonstrate reduction in vertebral fracture incidence. It is difficult to pool fracture data from different trials, in part because of the heterogeneity of study populations with respect to underlying disease, specific glucocorticoid treatment, or whether bisphosphonates were administered to prevent or to treat glucocorticoid-induced bone loss.

Calcium. Adequate calcium intake is needed to achieve maximal peak BMD in early and middle years and to maintain bone density in later life. However, calcium supplementation alone has not consistently shown reduction in fracture risk in postmenopausal or glucocorticoid-induced osteoporosis.

Commonly used supplements include calcium carbonate and calcium citrate. Calcium carbonate is best absorbed in an acidic environment, and therefore should be taken with food. It may also be less effective in persons using stomach acid-reducing medications such as H2-receptor blockers or proton pump inhibitors, though the clinical significance of this observation is unclear. Calcium citrate is generally more expensive than calcium carbonate, but does not require an acidic gastric pH for its absorption. The risk of nephrolithiasis does not increase in patients taking physiologic doses of calcium.

Vitamin D. Vitamin D refers to a group of fat-soluble steroid hormones and prohormones that influence calcium by their effects on intestine, kidneys, and bones. Cholecalciferol (D3) is produced by skin exposed to ultraviolet light and is the form of vitamin D present in fish. Both D3 and ergocalciferol (D2) can be synthesized and are used in vitamin supplements and to fortify foods, such as milk. D2 and D3 are converted to the active form of vitamin D, calcitriol (1,25-dihydroxyvitamin D), by hydroxylation first in the liver and then in the kidney.

In spite of multiple studies and meta-analyses, the effects of calcium and vitamin D on fracture risk remain unclear. Most studies that have shown vitamin D (along with calcium) to be effective in preventing fractures have used higher doses of vitamin D (800 IU daily, as opposed to 400 IU), and have included patients with lower baseline levels of vitamin D. The Women's Health Initiative examined the effects of calcium and vitamin D supplementation on a lower risk population, and found no fracture reduction in the intention-to-treat group. However, the women who were more compliant with their study medications did have a 29% reduction in hip fracture. In spite of the lack of definitive data, calcium and vitamin D supplementation remain standard of care in the treatment of osteoporosis.

The recommended daily allowance for vitamin D in older adults is 800-1000 IU, with most authorities recommend the higher dose. This amount is produced by sun exposure to hands, arms and face for 10-30 minutes a day 2-3 times a week during the summer months. Most multivitamins contain vitamin D, typically 400 IU. Many calcium supplements contain vitamin D, and most milk is vitamin D fortified. Vitamin D is fat-soluble, and thus toxicity can result from excess dosing. However, doses up to 4000 IU a day carry essentially no risk of toxicity.

The elderly, who may "get out" less and who have age-related reduction in the ability of skin to produce vitamin D, are at particular risk for vitamin D deficiency. Also at risk are those who reside at higher latitudes (e.g., Michigan), where the amount of UV light exposure during the winter is inadequate for vitamin D synthesis. Patients with malabsorption, renal insufficiency, liver failure, or other causes of secondary hyperparathyroidism or osteomalacia may require pharmacologic doses of specific forms of vitamin D and may benefit from referral to a specialist.

Bisphosphonates. Bisphosphonates are analogues of pyrophosphate, bind to hydroxyapatite crystals in bone, and inhibit resorption by effects on osteoclasts. Among all treatments for osteoporosis, bisphosphonates have the largest data set for reduction of fracture risk, including postmenopausal women, men, and in the setting of glucocorticoid use. Bisphosphonates are available in both

oral (alendronate, risedronate, and ibandronate) and intravenous (zoledronic acid and ibandronate) forms. While each of these medications has been shown to reduce fractures in placebo-controlled trials, comparative studies looking at fracture risk have not been done. A recent systematic review of therapy for osteoporosis concludes that each of the bisphosphonates reduces vertebral fractures, and that alendronate, risedronate, and zoledronic acid reduce hip fractures. Both risedronate and alendronate also reduce vertebral fractures in patients on chronic glucocorticoid therapy. A recent non-inferiority trial demonstrated similar effects on BMD with risedronate or zoledronic acid in patients receiving glucocorticoids.

Bisphosphonates have been associated with adverse effects. Oral bisphosphonates trials have reported esophageal complications ranging from heartburn and acid reflux to esophageal ulceration and perforation. Although these more serious complications are quite rare, patients with esophageal disorders may not be good candidates for oral bisphosphonates. It is also important to review the proper administration of oral bisphosphonates with patients. The FDA is currently investigating a possible connection between esophageal cancer and oral bisphosphonates.

Bisphosphonate use has been associated with musculo-skeletal pain, and this side effect has been included in the prescribing information for all drugs in this class. However, in January 2008, the FDA highlighted this risk, reminding clinicians to consider bisphosphonates when evaluating patients with musculoskeletal pain.

Zoledronic acid has been associated with a small increase in atrial fibrillation. The significance of this finding is difficult to interpret, as the overall rate of atrial fibrillation was equal in the treatment and placebo group. However, the incidence of atrial fibrillation felt to be "serious" was higher in the treatment group. More recently, a large trial comparing the incidence of atrial fibrillation in patients on oral bisphosphonates with case controls showed no difference. After a review of the available data on atrial fibrillation (November 2008), the FDA stated that "health-care professionals should not alter their prescribing patterns for bisphosphonates."

Osteonecrosis of the jaw (ONJ) has emerged as a more serious complication of high dose bisphosphonate therapy. ONJ is defined as an area of exposed bone on the maxilla, mandible, or palate that does not heal within eight weeks. Previously a rare occurrence, multiple cases have been reported since 2003, primarily in patients who received high doses of intravenous bisphosphonates in the setting of cancer treatment. Data from patients taking oral bisphosphonates for osteoporosis have been much more reassuring. The estimated risk of a patient on bisphosphonates for osteoporosis developing ONJ is estimated to be less than 1:100,000. Current recommendations suggest patients complete any necessary invasive dental work prior to beginning bisphosphonate therapy, particularly intravenous therapy.

Atypical femoral shaft fractures may also be associated with bisphosphonate use, and is being investigated by the FDA. These fractures tend to occur without trauma, and may be preceded by the sudden onset of thigh pain. The estimated risk of this complication is 1:10.000.

In light of their long half-lives, and effects on developing bone, the use of bisphosphonates in women of childbearing age should be discussed with an appropriate specialist. Bisphosphonates should not be used in women who are, or plan to become pregnant.

Denosumab. Denosumab is a human monoclonal antibody that binds to RANK ligand on the surface of osteoblast precursors, preventing them from activating osteoclasts. Administration of subcutaneous denosumab twice yearly to postmenopausal women with T-scores < -2.5 reduced fractures at spine (RR 0.32, 95% CI 0.26-0.41) and hip (RR 0.60, 95% CI 0.26-0.41). A comparison trial between denosumab and alendronate showed greater BMD increases in denosumab treated patients over 12 months. The study was not powered to evaluate differences in fracture risk. Denosumab is available for outpatient use, but only in clinic settings.

Denosumab is associated with an increased risk of cellulitis, although the risk is low (<0.5%). Other infections may be more common in patients on denosumab, An FDA REMS program is in place to monitor infectious and other complications.

Parathyroid hormone. Teriparatide, a recombinant protein containing the first 34 amino acids of human parathyroid hormone, is the only available anabolic agent for the treatment of osteoporosis. While parathyroid hormone, when secreted continuously (as in primary hyperparathyroidism) stimulates osteoclast activity, intermittent administration has a stimulating effect on osteoblast activity, resulting in increased BMD.

Teriparatide, in a randomized trial with 1,637 postmeno-pausal women, reduced vertebral fractures by 65% and nonvertebral fractures by 53%. No reduction occurred in hip fracture, but the total number was only 9. Teriparatide is given as a daily injection for 24 months, after which its beneficial effects on BMD tends to diminish. For this reason, a course of teriparatide is frequently followed by bisphosphonate therapy, as a way of "consolidating" gains. Teriparatide is also indicated for the prevention and treatment of glucocorticoid-induced osteoporosis. Interestingly, combining parathyroid hormone and alendronate may reduce the anabolic effects of the former.

Teriparatide was associated with an increased incidence of osteosarcoma in rats given high doses over an extended period. Given this concern, it should not be used in patients with a history of bony malignancy, or those at risk. Teriparatide use is typically reserved for patients with severe osteoporosis and pre-existing fractures. It may also

be considered in patients who have clinically failed bisphosphonate therapy, or are unable to tolerate bisphosphonates.

Raloxifene. Raloxifene is a nonsteroidal selective estrogen receptor modulator. It binds to estrogen receptors and inhibits bone resorption without significantly stimulating the endometrium. The Multiple Outcomes of Raloxifene Evaluation demonstrated a vertebral fracture relative risk of 0.7 after 3 years of use by postmenopausal women with osteoporosis (new vertebral fracture incidence ~5-7% with raloxifene, ~10% with placebo). A trend for reduction in non-vertebral or hip fracture risk did not reach statistical significance. Raloxifene use was also associated with a reduction in estrogen receptor-positive breast cancer incidence, but no increase in vaginal bleeding or breast pain. The risk of venous thrombosis is approximately the same as with estrogen replacement. No data have been reported for the use of raloxifene in glucocorticoid-induced osteoporosis. Raloxifene is not recommended for use in premenopausal women.

Estrogen. Estrogen acts directly on estrogen receptors in bone causing reduced bone turnover and bone loss. Estrogen is typically given as a single agent to women without a uterus, and with progestin to women who have not had hysterectomies. For many years, estrogen replacement therapy was routinely given to postmenopausal women. However the publication of the Women's Health Initiative (WHI) in 2002 demonstrated that postmenopausal estrogen therapy had both beneficial and deleterious effects.

One beneficial effect was a 34% reduction in hip fractures among the 8,506 women receiving estrogen and progestin. This was a particularly interesting finding in that the women in the WHI, while postmenopausal, were not selected for participation based on decreased bone density. Further analysis demonstrated a 35% reduction in vertebral fractures, a 29% reduction in wrist fractures, and a 24% reduction in total fractures. Given the size and design of the WHI, the overall bone health of its participants, and the reduction in fracture risk, a case can be made that estrogen has the best evidence supporting its role in fracture reduction in postmenopausal women.

Oral contraceptive pills may be used for osteoporosis prevention in premenopausal women with hypo-estrogenemic amenorrhea, especially those receiving gluco-corticoids. However, attention must also be paid to dietary issues, including the possibility of an eating disorder. The relationship between bone health and polycystic ovarian syndrome is debated, but premenopausal women with PCOS are generally not hypoestrogenemic and thus probably not at increased risk for osteoporosis.

Preparations and formulations identified as 'bioidentical hormones' do not have evidence demonstrating benefit in fracture reduction, or even safety, when compared to FDA-approved sources of estrogen. Considering that over 16,000 patients were needed to show clinical differences between estrogen and placebo in the WHI, it is unlikely that studies comparing estrogen with any 'bioidentical' formulation will be done in the foreseeable future. Women who wish to use 'bioidentical hormones' should be aware that they are using unproven therapy, from the perspectives of both safety and effectiveness.

Calcitonin. Calcitonin is a polypeptide hormone that inhibits osteoclast mediated bone resorption. The Prevention of Recurrence of Osteoporotic Fractures (PROOF) study, was of sufficient size (n=1,255), to demonstrate a reduction in vertebral fracture risk. However, the dropout rate was surprisingly high. Calcitonin does not appear to reduce the risk for hip fractures, other nonvertebral fractures, or fractures in patients on glucocorticoid therapy. Calcitonin, in small studies, has been found to reduce the pain of acute vertebral fractures.

Other Pharmacologic Therapies

Several other strategies may have some benefit in osteoporosis and deserve mention. Data regarding their benefits are, however, less robust and thus these strategies are not necessarily recommended at this time.

Combination therapy. Although combination therapy has theoretical appeal, multiple studies have yet to show a clinical benefit in combining anti-osteoporotic medications. As discussed above, combination therapy with parathyroid hormone and alendronate appears to blunt the anabolic effects of parathyroid hormone. Studies have also investigated the effects of combining bisphosphonate therapy with estrogen and raloxifene. While combination therapy, in some studies, results in an incremental increase in BMD, decreases in fractures have not been demonstrated. Combination therapy has a theoretical risk of oversuppression of bone remodeling ("frozen bone"), resulting in increased bone brittleness and fragility. However, this does not appear to have emerged as a clinical concern in long-term studies of bisphosphonate use. No guidelines exist for the use of combination therapy, however it may be worth considering for patients with significant, ongoing bone loss in spite of compliance with calcium, vitamin D, and a single anti-resorptive agent.

Calcitriol. Calcitriol (1,25-dihydroxy-vitamin D) is the active form of vitamin D, and is used in the management of hypocalcemia and metabolic bone disease associated with chronic kidney disease. It is effective in reducing the incidence of vertebral deformities. Side effects of calcitriol or high doses of other forms of vitamin D include hypercalcemia, hypercalciuria, and nephrolithiasis. Therefore serum and urinary calcium levels should be monitored by a specialist or other experienced provider.

Tamoxifen. In postmenopausal women tamoxifen has a small positive effect on BMD of the hip and spine. In premenopausal women, however, tamoxifen may cause a

significant decrease in BMD due to interference with estrogen. Tamoxifen has not been shown to reduce vertebral fracture risk.

Testosterone. Testosterone supplementation improves BMD in men who are taking glucocorticoids and have low serum testosterone. Testosterone replacement therapy should be strongly considered for younger men with definite hypogonadism. The role of testosterone therapy in older men is controversial given both the natural decline of testosterone levels and the increased prevalence of prostate disorders with aging. No well controlled studies support the use of supraphysiologic doses of testosterone for the treatment of osteoporosis. Testosterone supplementation for women does not appear to play a significant role in prevention of bone loss.

Thiazide diuretics. These diuretics affect bone metabolism by reducing urinary excretion of calcium. Hydro-chlorothiazide in doses as low as 12.5 mg per day in normotensive persons provides a modest but significant BMD benefit. Thiazide diuretics are also useful for treating bone loss due to calcium hyperexcretion. However, the routine use of thiazide diuretics for the treatment of osteoporosis is not recommended.

Phytoestrogens. Phytoestrogens, including isoflavones, are plant compounds that are converted to estrogens after ingestion. Soybeans, flaxseed, black cohosh, and red clover are the best known sources. Because of their estrogenic effects, they are postulated to have benefits for postmenopausal women. However, current data are inadequate to draw conclusions regarding the long-term benefits or safety of phytoestrogens.

Duration and Cessation of Pharmacologic Therapy

The optimal duration of bisphosphonate therapy for osteoporosis is not known. Ten-year data on alendronate therapy demonstrate its ongoing safety and effectiveness, although the study included only 164 alendronate-treated women. The long half-life of the bisphosphonates suggests that their effects may persist after discontinuing therapy. To address this issue, the FLEX trial randomized women who had been on alendronate for five years to receive five additional years of either alendronate or placebo. Women in the placebo group lost some BMD, but remained above their pre-alendronate baseline levels. No difference in overall fractures, or in vertebral fractures was detected radiologically. However, the placebo group did have a small increase in clinically detected vertebral fractures. This difference was largest in women with lower baseline BMDs or prior vertebral fractures, suggesting that women with milder osteoporosis might be able to discontinue bisphosphonates after five years of therapy, with appropriate monitoring of BMD.

Follow Up and When to Repeat DXA

When deciding if and when to repeat a DXA scan, consider the following:
- the patient's clinical risk factors for progression of bone loss and for fracture,
- the results from prior scans,
- whether a repeat DXA will change management,
- whether a repeat DXA result may improve compliance with therapy even if it will not change management.

Tables 5 and 8 summarize these and additional factors that may play a role in ongoing management and follow up.

Precision and reproducibility. Serial measurements should, if possible, be made with the same equipment. The precision error of DXA on the same machine, that is the reproducibility of a reading on repeat measurement, is approximately 1%. The 95% confidence interval on any measured change is therefore approximately ± 2.8%. This makes small changes difficult to detect reliably. For example, for a 2.0% decrease in DXA-measured BMD, the fairly large 95% confidence interval is -4.8 to +0.8%. Thus, small changes in BMD over a short period of time may be obscured by measurement-to-measurement variability.

BMD loss with usual aging is approximately 1% per year. The mean increase in lumbar BMD with treatment in various studies has typically been approximately 3% (range 0 to 10%) per yr. A change of 10% in BMD corresponds to a change of 1.0 in T-score.

Follow-up for average loss rate. Due to limits on precision and reproducibility of DXA scans, at least a two-year interval between scans provides more meaningful information on bone loss than a yearly DXA. This interval is also supported by an analysis of women who lost BMD during the first year of treatment with alendronate or raloxifene; these women were likely to gain during continued treatment. For example, women who took alendronate and lost more than 4% in hip BMD during the first year had an 83% chance of an increase in hip BMD during the second year. A similar phenomenon was seen even in those who received placebo. A case can also be made not to repeat DXA studies in patients with moderate bone loss, who are fracture-free on bisphosphonate therapy.

More frequent follow-up for high loss rate. Early in glucocorticoid use and after transplantation, when rate of bone loss can to be as great as 10% per year, repeating DXA at intervals of 6-12 months is appropriate for patients not on pharmacologic therapy.

Special Populations

Osteoporosis in Men

Osteoporosis in men is under-recognized and under-treated. One-third of all hip fractures occur in men, and the one-year mortality rate is twice that of women. An American College of Physicians Systematic Review identifies the following as risk factors for osteoporotic fractures: age greater than 70, BMI < 20-25 kg/m^2, weight loss in excess of 10%, physical inactivity, previous osteoporotic fracture, prolonged glucocorticoid use, and androgen deprivation therapy. Cigarette smoking was a risk factor for low BMD, and probably fractures; while alcohol use was a risk factor for fracture, with less definitive effects on BMD.

Men with one or more of these risk factors should probably be screened for osteoporosis by DXA. (FRAX may be helpful, with the caveat that the database is female-specific.) Since hypogonadism and vitamin D deficiency are both common in older men, laboratory assessment for both disorders is recommended. Treatment should include calcium and vitamin D supplementation along with weight bearing exercise, as tolerated. Bisphosphonates have been shown to reduce vertebral fractures as measured by radiological studies, and are considered first-line therapy in men with osteoporosis. Teriparatide has also been shown to reduce vertebral fractures. Denosumab increases BMD in men on androgen deprivation therapy for prostate cancer, but is not FDA-approved for routine use in male osteoporosis. Testosterone has been shown to increase lumbar spine BMD, but a reduction in fractures has not been shown. Given the potential complications of testosterone therapy in older men, it should be reserved for patients with clinically significant manifestations of hypogonadism.

Literature Search and Recommendations

The literature search for this update began with the results of the search performed for the 2002 version of this guideline. That search began with the results of a search performed by the National Osteoporosis Foundation (Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis), published in 1998 and including literature through 1996. Medline was then searched for literature from 1996 through 1999. Details of that search (similar to the update search explained below) were described in the 2000 guideline.

The search for the 2010 update of this guideline was performed on literature from 2000 through April 2007. The search was conducted prospectively using the major key words of: osteoporosis (including osteoporosis, postmenopausal); osteopenia; English language; and guidelines or controlled trials. Specific searches were performed for special risk categories (steroids, transplant, men/males/ non-Caucasian women/African-American women). For postmenopausal osteoporosis specific searches

were performed for risk factors (general risk factors, progestins, aromatase inhibitors, parathyroid), diagnostic testing (bone density scan/DXA, metabolic bone markers, bone quality, ultrasound), pharmacologic therapies (calcium, Vitamin D/ calcitriol, bisphosphonates, raloxifene, calcitonin, hormone replacement therapy, teriparatide, tamoxifen/SERMS, testosterone/androgens, thiazide diuretics, HMG-coA-reductase inhibitors, phytoestrogens, strontium), non-pharmacologic strategies (exercise, fall prevention), alternative and complementary therapies (phytoestrogens, isoflavanoids), and monitoring (DXA frequency). The detailed search strategy is available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent (through June 2009) clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

The review of literature was assisted by the publication in December 2007 of a systematic review of treatments: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis. The Agency for Healthcare Research published this review, which examined literature from 1966 through December 2006.

The 2011 interim revision of the guideline was based on literature reviews performed for recently published national guidelines and very recently recent (through July 2011) clinical trials known to expert members of the panel. The topic of denosumab was added.

Conclusions were based on prospective randomized controlled trials, if available, to the exclusion of other data. If RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was uses to estimate effect size. The "strength of recommendation" for key aspects of care was determined by expert opinion.

National Performance Measures

Centers for Medicare and Medicaid – Physician Quality Reporting Measures for Group Practice Reporting Option (GPRO):

- ACO Measurement # 64: Osteoporosis management in women who had a fracture - percentage of women 65 years and older who suffered a fracture and who had either a bone mineral density (BMD) test or prescription for a drug to treat or prevent osteoporosis in the 6 months after the date of fracture (GPRO)

- ACO Measurement # 63: Falls: Screening for fall risk - percentage of patients aged 65 years and older who were screened for fall risk at least once within 12 months - method of data collection GPRO

Related National Guidelines

This guideline generally conforms to:

American College of Obstetricians and Gynecologists. Osteoporosis. 2004, reaffirmed 2008.

American College of Physicians.
- Screening for osteoporosis in men. May 2008.
- Pharmacologic treatment of low bone density or osteoporosis to prevent fracture. Sep. 2008.

American College of Rheumatology. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Nov. 2010

Endocrine Society. Evaluation, Treatment, and Prevention of Vitamin D Deficiency. 2011.

National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. 2010.

U.S. Preventive Services Task Force. Screening for Osteoporosis. January 2011.

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who made to provide readers with information that might be of potential importance to their evaluation of the information.

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Van Harrison, PhD	(None)	
Robert Lash, MD	(None)	
Jane McCort, MD	(None)	
Jane Nicholson, MD	(None)	
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Acknowledgments

The following individuals are acknowledged for their contributions to previous versions of this guideline.

2002 (and 2005 interim revision): Jane T. McCort, MD, R. Van Harrison, PhD, Yolanda R. Smith, MD, Lourdes Velez, MD, Robert W. Lash, MD

Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, Geriatric Medicine, Metabolism and Endocrinology, and Obstetrics and Gynecology (Women's

Health). The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

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