Osteoporosis: Prevention and Treatment

Osteoporosis Guideline Team

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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 emission X-ray absorptiometry [DEXA] measures BMD.
A DEXA *T-score* is the number of standard deviations from mean BMD in young adult women.
Osteoporosis is defined as a DEXA 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 *[C]*.

Prevention

Recommend weight bearing exercise and adequate calcium (1200-1500 mg/day) and vitamin D (400-800 IU/day) across the life span (Table 6) *[D]*. Most older persons need vitamin D 700-800 IU/day *[A]*.

Risk Assessment and Diagnosis

Assess all adults for clinical risk factors for osteoporotic fracture (Table 2) *[C]*:

- Postmenopausal woman with one or more of the following:
  - Age ≥ 65 years
  - Low body weight
  - Personal history of fracture without substantial trauma age ≥ 40
  - Hip, wrist, or spine fracture without substantial trauma in 1st degree relative ≥ 50
  - Current smoking
  - Frailty
- Chronic glucocorticoid use (prednisone ≥ 7.5 mg daily, or equivalent, for ≥ 6 months).
- Organ transplant or pending transplant.
- Other associated medical conditions and medications.

Order DEXA based on clinical risk factors and potential impact of results on management (Table 3).
Evaluate appropriately and refer, when indicated, for secondary causes of osteoporosis (Table 4) *[D]*.

Treatment

Treat based on DEXA T-score and clinical risk factors for fracture (Tables 2 & 6):

- Prior osteoporosis-related fracture *[A]*.
- T-score ≤ -1 and (a) glucocorticoid use or (b) pending or post-transplant, especially if on steroids or (c) postmenopausal woman at high risk (i.e., with other risk factors for fracture but not already receiving hormone replacement therapy [HRT] *[A]*).
- T-score <-2 and (a) postmenopausal woman *[A]* or (b) man *[A]* or (c) person with other risk factors *[D]*.

When starting glucocorticoids consider therapy for prevention or treatment of osteoporosis *[A]*.
Base management strategies on benefits and risks (Tables 6,7, & 8):

- In post-menopausal women with osteoporosis:
  - Alendronate and risedronate reduce hip and vertebral fracture risk *[A]*.
  - Raloxifene and calcitonin reduce vertebral fracture risk *[A]*.
  - HRT reduces vertebral *[A]* and hip *[A]* fracture risk, but overall poses health risks ≥ placebo *[A]*. Consider use of HRT for osteoporosis only if there are other indications to use HRT.
- In men with osteoporosis alendronate reduces vertebral fracture risk *[A]*.
- In glucocorticoid use risedronate (and perhaps alendronate) reduces vertebral fracture risk *[A]*.

Follow-up

Follow-up osteoporosis or osteopenia with a repeat DEXA based on a patient's situation (Tables 3 & 5).
For most persons an interval of ≥ 2 years between DEXAs provides the most meaningful information.
Early in glucocorticoid use and/or after transplantation consider repeating DEXA in 6-12 months.

*** 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 [WHO] Definitions

Classification	DEXA T-score (SD from young normal)
Normal	≥ -1.0
Osteopenia	> -2.5 but < -1.0
Osteoporosis	≤ -2.5

Table 2. Clinical Risk Categories for Osteoporosis and Osteoporotic Fractures (for use with Table 3)

Extremely High Risk

Prior osteoporotic fracture [a]
(fracture in absence of significant trauma)

Very High Risk

Glucocorticosteroid use[b]
(prednisone ≥ 7.5 mg/d, or equivalent, for ≥ 6 months)

Solid organ transplant [c]
(awaiting or following, especially within 2-3 yrs after)

High Risk

Postmenopausal with ≥1 of[d]:
- Age 65 years or greater
- Personal history of fracture without substantial trauma ≥ age 40
- Family history of fracture (hip, wrist, or spine in first-degree relative ≥ age 50)
- Current smoking
- Weight in lowest quartile (< 57.8 kg or 127 pounds)
- Frailty (inability to rise from chair unassisted)

Moderate Risk

Postmenopausal not taking estrogen and no higher level risk factors

Family history of osteoporosis

Medications:
- Cyclosporine A
- GnRH therapy (leuprolide (Lupron®), goserelin (Zoladex®), and others)
- Anticonvulsants (phenytoin, phenobarbital > carbamazepine, valproic acid; gabapentin probably no risk)
- Heparin (unfractionated > LMWH)
- Tacrolimus (FK506, Prograf®)
- Tamoxifen before menopause
- Inhaled glucocorticoids, high dose and/or prolonged duration
- Medroxyprogesterone acetate injectable suspension (Depo-provera®)[e]
- Aromatase inhibitors (anastrozole [Arimidex®], letrozole [Femara®], exemestane [Aromasin®])

Conditions with significant association:
- Alcoholism
- Cushing's syndrome
- Gastrectomy
- Hypogonadism, including due to medication, surgery, or chemotherapy
- Hemochromatosis
- Hyperparathyroidism, primary or secondary
- Inflammatory bowel disease (Crohn's > ulcerative colitis)
- Severe liver disease (especially primary biliary cirrhosis)
- Multiple myeloma
- Malabsorption
- Rheumatoid arthritis
- Premenopausal amenorrhea except PCOS (e.g., anorexia nervosa, exercise, hyperprolactinemia)

Some Risk

Postmenopausal taking estrogen and no higher level risk factors

Conditions with possible association:
- Addison's disease
- Amyloidosis
- Diabetes mellitus, type 1
- Thalassemia (major > minor)
- Multiple sclerosis
- Nephrolithiasis
- Thyrotoxicosis
- Sarcoidosis

Risk Factors for Falling
- Use of any benzodiazepine or sedative/hypnotic agent
- Frailty
- Environmental hazards for falls
- History of falls
- Impaired vision
- Impaired cognition
- Impaired gait, balance or transfer skills
- Impaired leg or arm muscle strength or range of motion
- Low physical function
- Postural hypotension

[a] Prior fracture is more predictive of future fracture than is bone mineral density [BMD].
[b] Glucocorticoids produce the greatest bone loss in the initial 6-12 months of use, average of 4-5%.
[c] Bone loss can be as much as 10% in the first year after transplant.
[d] Early in menopause, including after bilateral oophorectomy, bone loss is more rapid in the spine than the hip.
[e] Bone loss greater w/ increasing duration of use, probably greatest in first 2 years, and may not be completely reversible.

Table 3. Screening and Management Based on Risk Factors for Osteoporosis and Osteoporotic Fractures

Clinical Risk (from Table 2)	**First DEXA** [a]	**Management Based on T-score from First DEXA** [b]		
		< -2	**-2 to -1**	**> -1**
Extremely High	DEXA not required for diagnosis. Order only if it will help follow response to treatment or guide treatment changes.	Treat: Yes. 2nd DEXA: Only if results will change treatment.	Treat: Yes. 2nd DEXA: Only if results will change treatment.	Treat: Yes, but first carefully consider other cause of fracture, e.g., malignancy. 2nd DEXA: Only if results will change treatment.
Very High	Order DEXA.	Treat: Yes. If on estrogen, change or add therapy. 2nd DEXA: 6–12 mo.	Treat: Yes. If on estrogen, consider changing or adding therapy. 2nd DEXA: 6–12 mo.	Treat: Consider preventive therapy. 2nd DEXA: 6–12 mo.
High	Order DEXA.	Treat: Yes. If on estrogen, consider changing or adding therapy. 2nd DEXA: ≥ 2 yrs.	Treat: Consider treating. If on estrogen, consider changing or adding therapy. 2nd DEXA: ≥ 2 yrs.	Treat: No. Reassess clinical risk in 1 year. 2nd DEXA: 3–5 yrs unless change in risk status.
Moderate	Consider DEXA, especially if risk for falling (Table 2). If not ordered, reassess clinical risk in 1 year.	Treat: Yes. If on estrogen, consider changing or adding therapy. 2nd DEXA: ≥ 2 yrs.	Treat: Consider treating. If on estrogen, consider changing or adding therapy. 2nd DEXA: ≥ 2 yrs.	Treat: No. Reassess clinical risk in 1 yr. 2nd DEXA: 3-5 yrs unless change in risk status.
Some (all others)	Reassess clinical risk in 1 yr.	(No first DEXA.)	(No first DEXA.)	(No first DEXA.)

Note: DEXA $100-406. 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 DEXA only if results will affect management, e.g., not already receiving full therapy, or starting or stopping estrogen.

[b] Lowest T-score from femoral neck, greater trochanter, total hip, or any lumbar vertebra. Wards triangle is less predictive of fracture risk *[D]*.

Table 4. Evaluation for Secondary Causes of Osteoporosis and Osteopenia *[D]*

All patients: consider calcium, alkaline phosphatase, renal function, liver function tests [Comprehensive metabolic panel $15-50], TSH [$23-71]

Men: consider testosterone [Free: $35-120, Total: $36-125] (1/3 of older men with osteoporosis have hypogonadism *[C]*)

Premenopausal with amenorrhea not due to polycystic ovary syndrome: estradiol & FSH [$65-209] (hypogonadal)

Based on clinical situation:

- Intact-PTH [$57-187] with calcium [$7-21] (hyperparathyroidism, primary or secondary)
- 24h urine free cortisol [$23-99] or 1 mg dexamethasone suppression [$23-70] (hypercortisolism)
- 25-hydroxy-vitamin D (osteomalacia) [$41-66]
- Evaluation for occult malignancy, e.g., multiple myeloma, bony metastases

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.

Table 5. Considerations for Subsequent DEXA

Assess:

- Number and types of risk factors, Table 2.
- Results from prior DEXAs.
- If transplant patient, time since transplant. (Highest risk for fracture is within first 2-3 years following transplant *[C]*.)
- Overall context, e.g., patient life expectancy.

Repeat DEXA:

- Only if results will change management.
- If BMD not ↑ing, stable, or ↓ing slowly.
- After starting, stopping, or changing antiresorptive therapy [*].

Use intervals suggested for 2nd DEXA in Table 3.

[*] Antiresorptive therapies include, alendronate, risedronate, raloxifene, estrogen, and calcitonin.

Table 6. Pharmacologic Therapy for Osteoporosis Treatment and Prevention

AGENT		DOSE	COST/30 DAYS* Generic	COST/30 DAYS* Brand	OTHER CONSIDERATIONS
All Adults					
Calcium (as elemental calcium)		Total daily intake 1000-1500 mg	$6-8	$8-16	• Constipation is common • Nephrolithiasis is not a contraindication • ↑s BMD but not shown to ↓ fracture postmenopause or w/ steroid use *[A]*
Vitamin D		Total daily intake 700-800 IU	$2-5		• 700-800 (but not 400) IU/day ↓s hip fracture in older men & women *[A]* • 10-30 min sun exposure to arms & face 2-3x/week = 400 IU/day • For high doses or calcitriol consider specialist consultation
Treatment, listed in decreasing order of approximate quality and quantity of data supporting efficacy					
Bisphosphonates					• Take ≥ 30 min before 1st food of day w/ 8 oz water then upright ≥ 30 min • Mild GI effects excess 0-5% cf. placebo; rare severe GI effects • Reflux w/o esophagitis is relative but not absolute contraindication • Renal excretion, thus avoid if creatinine clearance <30-35 • Safety not known for women during child bearing years
Risedronate (Actonel®)	treatment	5 mg po daily		$78	
	treatment	35 mg po weekly		$72	
Alendronate (Fosamax®)	treatment	10 mg po daily		$78	
	treatment	70 mg po weekly		$72	
	prevention	5 mg po daily		$78	
Raloxifene (Evista®)		60 mg po daily		$86	• 70% ↓ breast cancer risk; incidence 0.4% treated, 1.2% not *[A]* • DVT/PE risk approximately same as HRT *[A]* • No ↑ risk of endometrial cancer compared to placebo *[A]* • 5-10% ↓ levels total cholesterol & LDL; no effect HDL or triglycerides • Hot flash incidence 3-6% greater than placebo • Not recommended for men or for premenopausal women
Hormone Replacement Therapy [HRT]					• Estrogen + progestin *[A]* - ↑ Risk†: CHD, stroke, breast cancer, DVT, PE - ↓ Risk†: hip fracture, vertebral fracture, colon cancer - Breast cancer ↑ risk probably not significant until ≥ 5 yrs of therapy - Breast cancer risk probably returns to baseline 5 yrs. after stop treatment • Estrogen alone *[A]* - ↑ Risk†: stroke, DVT [no effect on risk PE] - ↓ Risk†: hip fracture, vertebral fracture • Hot flash frequency ↓ by >75% compared to placebo *[A]* • Likely worsens existing & ↑ risk new urinary incontinence *[A]* • Gall bladder disease risk ↑ ~60% (20-30 excess cases 10000 pt-yrs) *[A]* • Unopposed estrogen ↑ risk of endometrial cancer *[C]*
Estrogens					
Estradiol (Estrace®)		1 mg po daily	$9	$31	
Esterified estrogens (Estratab®)		0.625 mg po daily		$19	
Estropipate (Ogen®)		0.625 mg po daily		$27	
Conjugated estrogens (Premarin®)		0.625 mg po daily		$31	
Transdermal estradiol (various)		0.05 mg/d 1-2x/wk	$40	$73	
Progestins					
Medroxyprogesterone (Provera®)		02.5-5 mg daily	$7-10	$20-31	
Micronized progesterone (Prometrium®)		100-200 mg daily		$35-66	
Combinations (various)					
Prempro™		0.625/2.5 mg daily		$40	
Calcitonin Nasal Spray (Miacalcin®)		200 IU daily, alt nostrils		$89	• Rhinitis 5% excess compared to placebo *[A]* • Caution in renal failure • Reduces pain of acute fracture *[A]*

Note: CHD=Coronary Heart Disease; DVT=Deep Venous Thrombosis; GI=Gastrointestinal; PE=Pulmonary Embolism; RF=Risk Factor.

***** Brand drugs=Average Wholesale Price minus 10% AWP from Amerisource Bergen Wholesale Catalog 6/4/05. Generic=maximum allowable cost +$3 from BCBS of MI MAC list 5/25/05.

†Number in parentheses following each outcome represents absolute excess or reduction in cases of that outcome per 10000 pt-yrs of treatment compared to placebo.

Table 7. Evidence* for Effect of Therapy on Osteoporosis [OP] Related Outcomes by Patient Group

Pharmacologic Therapy	Patient Group			
	Postmenopause, any	Postmenopause, w/ OP	Men, w/ OP	Glucocorticoid Use
Calcium with Vitamin D	↑ BMD *[A]*	↓ hip fracture *[A]* (if patient vitamin D deficient)	↑ BMD *[A]*	↑ BMD *[A]*
Alendronate	↑ BMD *[A]*	↓ hip fracture *[A]* ↓ spine fracture *[A]*	↓ spine fracture *[A]*	↑ BMD *[A]* (trend ↓ spine fracture *[A]*)
Risedronate	↑ BMD *[A]*	↓ hip fracture *[A]* ↓ spine fracture *[A]*	(no data)	↓ spine fracture *[A]*
Raloxifene	↑ BMD *[A]*	↓ spine fracture *[A]* (trend ↓ non-spine fracture *[A]*)	(no data)	(no data)
Estrogen	↓ hip fracture *[A]* ↓ spine fracture *[A]*	↓ hip fracture *[A]* ↓ spine fracture *[A]*	(no data)	↑ BMD *[A]*
Calcitonin	↑ BMD *[A]*	↓ spine fracture *[A]*	(no data)	↑ BMD *[A]* (trend ↓ spine fracture *[A]*)

* 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 8. Number of persons Needed to Treat[a] with a given therapy and duration to prevent one event.

Reference	Subjects	Therapy	Yrs	Event	NNT (95% CI)
Chapuy et al. NEJM 1992. [France]	elderly pmw, no Fx, no HRT	calc & vit D	1.5	hip Fx	48 (25, 485)
Liberman et al. NEJM 1995.	pmw, OP but no hip Fx	alendronate	3	VFx	34 (17, 2705)
Black et al. Lancet 1996. [FIT, Fx arm]	pmw, FN-T ≤ -2 & ≥ 1 VFx	alendronate	3	VFx	35 (22, 87)
Black et al. Lancet 1996. [FIT, Fx arm]	pmw, FN-T ≤ -2 & ≥ 1 VFx	alendronate	3	hip Fx	86 (43, 10971)
Orwoll et al. NEJM 2000. [men]	men, OP or osteopenia[b]	alendronate	2	VFx	16 (8, 162)
Harris et al. JAMA 1999. [VERT]	pmw, VFx	risedronate	3	VFx	20 (12, 62)
Harris et al. JAMA 1999. [VERT]	pmw, VFx	risedronate	3	non-VFx	43 (22, 569)
Wallach et al. Cal Tis Int 2000.	prednisone ≥ 7.5 mg daily	risedronate	1	VFx	9 (5,36)
Ettinger et al. JAMA 1999. [MORE]	pmw, VFx	raloxifene	3	VFx	15 (10, 38)
Ettinger et al. JAMA 1999. [MORE]	pmw, OP but no Fx	raloxifene	3	VFx	47 (29, 121)
Cummings et al. JAMA 1999. [MORE]	pmw, OP or VFx	raloxifene	3	invasive BrCA	126 (83, 265)
Cauley et al. JAMA 2003. [WHI]	pmw	estrog+prog	~5	hip Fx	345 (181, 3918)
WHI Steering Com. JAMA 2004. [WHI]	pmw	estrog alone	~7	hip Fx	216 (121, 1027)
Chestnut et al. Am J Med 2000. [PROOF]	pmw, VFx, T ≤ -2, no hip Fx	calcitonin	3	VFx	12 (7, 76)

Note: BrCA=breast cancer; FN=femoral neck; Fx=fracture; OP=osteoporosis; pmw=postmenopausal women; VFx=vertebral fracture.
[a] Number Needed to Treat [NNT] is the inverse of Absolute Risk Reduction, NNT = 1/ARR.
[b] OP Fx or FN-T ≤ -2.

Clinical Background

Clinical Problem

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, there are effective strategies for prevention and treatment.

Incidence and risks. Ten million people in the United States have osteoporosis and an additional 18 million have low bone mass. Gender, age, and race are important risk factors for osteoporotic fractures. In the United States, approximately 30% of postmenopausal white women have osteoporosis. In women over the age of 80, the prevalence of osteoporosis is as high as 70% and 25% have had at least one vertebral fracture. The lifetime probability of a hip

fracture for an average Caucasian woman is 14%; the risk for a Caucasian man or an African-American woman or man is roughly one-third to one-half that, i.e., 5-7% *[C]*.

Certain medications, particularly glucocorticoids, and various medical conditions, including renal failure, hypogonadism, and alcoholism, are important secondary causes of osteoporosis. For example, as many as 50% of persons using glucocorticoids long-term sustain an osteoporotic fracture. Some studies report fractures in 2/3 of patients in the first year after organ transplantation.

Morbidity, mortality, and cost. An osteoporotic hip fracture can result in up to 10-20% excess mortality within 1 year. Furthermore, 50% of all women with hip fractures spend some time in a nursing home, 25% of patients with hip fractures may require long-term nursing care, and only 30-50% fully regain their prefracture level of independence. Osteoporotic fractures may also result in chronic pain, disability, deformity, and/or depression. In 1995, direct medical costs for treatment of osteoporotic fractures were approximately $14 billion. It is believed that there are significantly greater indirect costs.

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. Although there are currently no practical methods to assess overall bone strength, bone mineral density [BMD] correlates closely with skeletal load-bearing capacity and fracture risk. The World Health Organization [WHO], therefore, developed definitions based on BMD measurements. A *T-score* is the number of the standard deviations [SDs] from the mean BMD in young adult women. *Osteoporosis* is defined as T-score at any site of -2.5 or lower, while *osteopenia* is defined as a T-score between -1 and -2.5.

While there are no standard diagnostic criteria for osteoporosis in men, most use the WHO criteria, that is T-score of ≤ -2.5 relative to normal young women. Although men have much higher baseline BMD than women, they seem to have similar fracture risk for a given BMD.

Etiology and Natural History

Normal bone loss. Bone remodeling is an ongoing, cyclic process of bone formation and resorption. *Osteoclasts* adhere to bone and remove it, while *osteoblasts* secrete osteoid and help rebuild bone. Bone loss can occur if there is an imbalance between these two processes. All currently FDA approved therapies for osteoporosis are antiresorptive, although other therapies are being investigated.

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.

Bone density in later life depends more or less equally on peak mass achieved in youth and on subsequent rate of loss. Skeletal mass is maximal in approximately the fourth decade of life and depends primarily on diet (especially calcium and vitamin D), physical activity, and genetics. During the first few years after menopause women may 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.

Glucocorticoid related bone loss. The etiology of glucocorticoid-induced osteoporosis and associated fractures is not fully understood, but is complex, multifactorial and in some ways 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 homeostasis is affected by a decrease in gastrointestinal absorption and an increase in urinary loss. Also, glucocorticoids inhibit production of sex steroid hormones in both men and women, which in turn affects the bone remodeling cycle. Bone loss is most rapid during the first 6 to 12 months of therapy and, as in early menopause, trabecular bone is affected more than cortical *[C]*. 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 *[C]*. 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.

Clinical Risk Factors

Assessment of clinical risk factors for low bone density and fracture may help identify those who would benefit from further evaluation with quantitative measurement of BMD (see Tables 2 and 3). Such risk factors, however, have been most studied in Caucasian women and account for only 20-40% of variability in BMD. Although several prediction models have been proposed, none has performed consistently well.

Caucasian women. In community-dwelling Caucasian women age 65 years and older, osteoporotic fracture is significantly correlated with: increasing age; personal previous fracture of any type after age 50; maternal history of hip fracture; long-acting benzodiazepine or anticonvulsant drug use; previous hyperthyroidism; ingestion of large amounts of caffeine; standing four hours or less per day; slow rise from a chair; poor vision; and resting tachycardia. 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 *[C]*.

African-American women. Risk factors for hip fracture in African-American women age 45 years and older include: lowest quintile in body mass index [BMI]; use of aids in walking; history of stroke; and consumption of seven or more alcohol drinks per week *[C]*.

Falls. Approximately one-third of community-dwelling elderly 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 and/or a fall laterally with direct impact to the hip *[C]*.

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 *[D]*.

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 *[C]*. Lower doses for extended periods and even prolonged use of inhaled steroids may cause abnormal bone loss *[C]*. Alternate day dosing has not been shown to produce less bone loss than daily use *[C]*.

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 *[C]*. This is most likely due to greater steroid use, although other medications, such as cyclosporine-A and tacrolimus, may be factors *[C]*.

Men. Little data are available regarding osteoporosis and associated fractures in men, but risk factors appear to be similar to those for women *[C]*. As many as a third of older men with osteoporosis have a low testosterone level *[C]*. For unclear reasons, men with hip fractures have a higher mortality than women *[C]*. It may be 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.

Diagnostic Testing

Bone density compared with other common screening. BMD is at least as effective for predicting fracture as is screening for hypercholesterolemia or hypertension in relation to heart disease. When BMD is -1 SD the relative risk for fracture is 1.5-2.0. A cholesterol at +1 SD confers a relative risk of 1.3 for a cardiac event and 1.5 for cardiac death, while a diastolic blood pressure of +1 SD is associated with a relative risk of 1.5 for cardiac death.

Dual emission X-ray absorptiometry [DEXA]. Dual emission X-ray absorptiometry is currently the test of choice for measuring BMD. The technique compares penetration of two different X-ray frequencies through soft tissue and bone, then 'subtracts' soft tissue, leaving an estimate of skeletal BMD. A study typically takes less than 10 minutes, and radiation exposure is about 1 mrem/site. By comparison, background radiation is about 1 mrem/day.

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

BMD measurement by DEXA 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, M-CARE, and most other major insurers cover DEXA for patients at risk, including all women age 65 years or greater and patients with primary hyperparathyroidism, vertebral abnormalities, or chronic glucocorticoid use. Medicare does not cover BMD testing for premenopausal women or for postmenopausal women less than 65 years of age receiving estrogen. Follow-up studies are covered, usually at two-year intervals, though more frequently when indicated (e.g., chronic glucocorticoid use). Medicare will cover a follow-up BMD test every two years (> 23 months since last BMD test) to monitor response in those patients undergoing FDA-approved treatment of osteoporosis.

Other diagnostic and monitoring modalities. Quantitative ultrasound, usually of the calcaneus, is less expensive and more portable than DEXA, and is being used in large osteoporosis screening programs. Prospective data suggest that it can predict fracture risk at the hip. T-scores

provided by ultrasound, however, are not equivalent to DEXA T-scores, and patients with abnormally low ultrasound T-scores should be evaluated by DEXA for more definitive diagnosis.

Biochemical markers of bone resorption are used in research settings to assess the effect of antiresorptive therapy, with benefit usually resulting in decreased marker levels over two to three months *[A]*. They are not, however, predictive of BMD or fracture risk, and their use in general practice is not recommended.

Prevention

General prevention. Encourage all patients to: eat a balanced diet that includes adequate calcium and vitamin D (using supplements when necessary); engage in regular physical activity; avoid heavy alcohol consumption; and refrain from smoking.

Glucocorticoid-induced osteoporosis prevention. Use the lowest effective daily dose for the shortest period. When possible, use inhaled or topical rather than oral preparations. Every other day dosing has not been shown superior to daily dosing with respect to bone loss *[C]*. Bisphosphonates prevent and treat glucocorticoid related bone loss at both the lumbar spine and femoral neck *[A]*. They also reduce risk of vertebral fracture *[A]*. Calcium with vitamin D (although probably not calcium alone) and calcitonin prevent vertebral bone loss during glucocorticoid therapy *[A]*.

Evaluation of Secondary Causes

Although most cases of osteoporosis are idiopathic, there are several secondary causes, Table 2. Many of these are treatable (e.g., hypogonadism, hyperparathyroidism, malabsorption) or are at least important to diagnose (e.g., renal failure, multiple myeloma), thus a focused evaluation is usually indicated, Table 4. Consider secondary hyperparathyroidism (normal or low calcium with elevated parathyroid hormone) in patients with renal insufficiency and/or when inadequate intake or absorption of calcium or vitamin D or both is 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 *[C]*.

Whom to Treat

When deciding whom to treat, consider a patient's ongoing risk for bone loss and fracture as well as BMD. T-scores should be viewed as continuous variables in relation to fracture risk. In general, patients with T-scores less than -2.0 should be treated. Although these persons may not meet the WHO definition (Table 1) for frank osteoporosis, they are nonetheless at risk for both ongoing bone loss and fractures. Similarly, patients with T-scores less than -1 who have additional risk factors, for example glucocorticoid use or significant liver disease, should be treated. Finally, patients who have already had an osteoporotic fracture may be treated on that basis alone *[A]*, although a DEXA may be useful in other aspects of their management.

Main Pharmacologic Therapies.

The best trial endpoints for osteoporosis therapies are clinical, specifically fracture incidence. Although low BMD is an excellent predictor of fracture risk in postmenopausal women, increase in BMD as a surrogate endpoint has shown an inconsistent relationship to fracture. It appears that each of the available classes of antiresorptive agents (bisphosphonates, SERMs, estrogens, and calcitonin) demonstrates similar reduction in vertebral fracture rates in postmenopausal women, independent of effects on BMD *[A]*. Therefore, recommended and FDA approved therapies for osteoporosis are those with strong data for reduction in fracture risk, Tables 7 and 8.

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 and have probably been insufficiently powered to demonstrate reduction in 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 and glucocorticoid treatment. Also, some studies evaluate therapy for primary prevention, i.e., initiated approximately at the same time as glucocorticoid, while others evaluate secondary prevention (treatment), i.e., therapy started in the setting of osteoporosis at some later point during glucocorticoid administration.

Calcium. Adequate calcium intake is needed to achieve maximal peak BMD in early and middle years and to maintain bone in later years. Calcium supplementation of at least 400 mg/day in postmenopausal women is associated with a small but significant increase in BMD [A] and a trend toward reduction in vertebral fracture risk. Overall, calcium supplementation has not been shown to affect risk of fracture in postmenopausal women, men, or in persons taking glucocorticoids. Nonetheless, since many people in the United States do not consume the recommended amounts of calcium, addressing intake is recommended.

Commonly used supplements include calcium carbonate (ranging from 200 mg calcium/500 mg tablet to 500 mg calcium/1250 mg tablet) and calcium citrate (200 mg/900 mg tablet). Calcium carbonate is best absorbed in an acidic setting, thus it should be consumed with food and is somewhat less effective in persons using medications such as ranitidine or omeprazole. Calcium citrate, although generally more expensive than calcium carbonate, is

effective regardless of gastrointestinal pH. The risk of nephrolithiasis, even in those with a history of kidney stones, does not appear to increase in patients taking physiologic doses of calcium, although more than 2000 mg of elemental calcium daily may impart risk *[C]*.

Vitamin D. Vitamin D refers to a group of fat-soluble steroid hormones and prohormones that influence calcium by effects on intestines, kidneys, and bones. Cholecalciferol (D3) is produced by skin exposed to ultraviolet light and is also available from dietary animal sources, particularly fish and egg yolks. Ergocalciferol (D2) can be synthesized from plant sources and is used to fortify foods. D2 and D3 are converted to active forms, primarily calcitriol (1,25-dihydroxyvitamin D), by hydroxylation in the liver then the kidney.

For adults, the minimum recommended adequate intake of vitamin D is 200-600 IU/day. Many recommend 400-800 IU/day. Sun exposure to hands, arms and face for 10-30 minutes per day 2-3 times per week can be equivalent to 400 IU/day. The effect of sun on vitamin D depends on skin color, season, latitude, cloud cover, and a number of other factors. Most multivitamins contain 400 IU of vitamin D. Many calcium supplements contain vitamin D, and most milk is vitamin D fortified (125 IU per 8 oz). Vitamin D is fat-soluble and thus excess intake can cause toxicity. The recommended tolerable upper intake level for vitamin D is 2000 IU/day. Sun exposure is unlikely to result in vitamin D toxicity.

Vitamin D supplementation at relatively high doses (700-800 IU/day) but not at lower doses (400 IU/day) reduces risk of hip fracture among older (≥ age 60, mean age 80 years) men and women *[A]*. Without concurrent calcium supplementation however it has not been associated with reduction in hip fracture incidence among postmenopausal women *[A]*.

In patients taking steroids, vitamin D and calcium together prevent bone loss when compared to calcium alone or placebo *[A]*. There are insufficient data to show decrease in fracture risk in this population.

The elderly, who may "get out" less and who have age-related reduction in the ability of skin to produce vitamin D, are at risk for vitamin D deficiency. Also at risk are those who reside at higher latitudes during the winter (e.g., Michigan), where UV light in winter months is inadequate for vitamin D synthesis *[C]*. 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. In high doses, they also inhibit mineralization, which can be detrimental to bone strength. The more potent bisphosphonates, such as alendronate and risedronate, can be given in doses small enough to have little if any effect on mineralization.

Bisphosphonates have been studied in multiple, large randomized controlled trials, involving in all more than 10,000 people. Among all treatments for osteoporosis, the strongest data for reduction of fracture risk are for these agents, including both alendronate and risedronate in postmenopausal women, men, and in the setting of glucocorticoid use.

Alendronate and risedronate in postmenopausal women with osteoporosis each reduce risk for vertebral and hip fracture by 30-50% *[A]*. In similar patients alendronate 70 mg weekly and 10 mg daily produce comparable improvement in BMD at both spine and hip *[A]*. Studies of weekly therapy have been too small to assess fracture endpoints.

In men and women taking glucocorticoids alendronate and risedronate improve spine and hip BMD, regardless of steroid duration or dose, underlying disease, and baseline lumbar BMD *[A]*. A study of risedronate in similar patients showed a significant reduction in incidence of new vertebral fractures, (~16% placebo vs. ~5-6% treatment) *[A]*. A smaller study with alendronate found a similar trend (~7% placebo vs.~1% treatment) *[A]*.

In men with osteoporosis alendronate improves BMD and reduces risk for vertebral fracture. After two years 1% of treated patients and 7% of controls had vertebral fractures *[A]*. No data demonstrate reduction in nonvertebral fracture risk, but this lack of evidence is most likely due to study size *[D]*.

The safety of bisphosphonates for women in childbearing years and in pregnancy is not known.

Raloxifene. Raloxifene is a nonsteroidal selective estrogen receptor modulator [SERM]. It binds to estrogen receptors and inhibits bone resorption without significantly stimulating the endometrium.

The Multiple Outcomes of Raloxifene Evaluation [MORE] (n=7705) 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]*. There was a nonsignificant trend for reduction in non-vertebral fracture risk. Raloxifene use was also associated with a reduction in breast cancer incidence, but no increase in vaginal bleeding or breast pain *[A]*. 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.

Hormone replacement therapy [HRT]. Hormone replacement therapy may be either estrogen in combination with a progestin or estrogen alone, usually for a woman without a uterus. Conventional belief, based primarily on observational data, has been that HRT provides more benefit than risk for most postmenopausal women. It is very effective in relieving menopausal symptoms such as hot flashes, night sweats, and genitourinary atrophy *[A]*. However, a recent very large randomized controlled trial, the Women's Health Initiative [WHI], found that although HRT was associated with decreased risk for hip and vertebral fractures, when considering a number of other major medical conditions, combined HRT posed more risk than benefit. For estrogen alone, the benefits and risk seemed to be approximately equal to risk *[A]*.

In the Women's Health Initiative estrogen combined with progestin was associated with an increased risk of coronary heart disease, stroke, invasive breast cancer, and venous thromboembolism. There was a decrease in risk of hip fracture, vertebral fracture, and colon cancer. When benefits and risks were combined, there was an overall excess of adverse events of 19 per 10,000 women-years of estrogen plus progestin therapy.

In the same study, estrogen alone compared to placebo was associated with an increased risk of stroke and deep venous thrombosis (but not pulmonary embolus). There was a decrease in risk of hip fracture and vertebral fracture but no statistically significant effect on coronary heart disease. Overall, there was a nonsignificant excess in adverse events of 2 per 10,000 woman-years with unopposed estrogen.

Estrogen plus progestin and estrogen alone (each compared to placebo) were associated with approximately one third fewer hip and vertebral fractures. The absolute risk reduction was 11-12 fractures per 10000 women-years of therapy.

The WHI was not designed to evaluate HRT as "treatment" for osteoporosis, and, in fact, the presence or absence of osteoporosis was not known for most women. Bone density, however, was measured for a small subgroup (~6%), among which only about 5% had osteoporosis (suggesting that osteoporosis "prevention" was the outcome being studied. Over 3 years, women assigned to use of estrogen with progestin had a significant improvement in BMD at hip and spine. Those with placebo had no significant change at hip and slight improvement at spine. When women were stratified by various risk factors for osteoporosis and by presence of osteoporosis (based on T-scores) the effect of therapy did not significantly differ.

In an ancillary study, Women's Health Initiative Memory Study [WHIMS], there was a small increase in risk of dementia and mild cognitive impairment for those women over age 65 who took estrogen, either combined or alone, compared to placebo *[A]*. This is not inconsistent with the findings of several other small earlier studies that overall were inclusive.

WHI data and other studies suggest that HRT raises risk for gall bladder disease, specifically cholelithiasis, cholecystitis, and cholecystectomy. Also, (contrary to common belief) HRT seems to be associated with increased risk of new urinary incontinence or worsening of existing urinary incontinence. Estrogen alone for a woman with a uterus increases the risk of endometrial cancer, although adding a progestin reduces the risk to baseline.

In summary, HRT, combined or estrogen alone, for postmenopausal women decreases risk for hip and for vertebral fractures, but increases risk for a number of other significant medical conditions. Thus, HRT should not be prescribed for osteoporosis unless a woman has other other indications for use, such as menopausal symptoms, and has low risk for the conditions associated with increased risk.

Oral contraceptive pills may be used for osteoporosis prevention in hypoestrogenemic amenorrhea in premenopausal women, especially those receiving glucocorticoids. However, Depo-Provera now carries "Black Box" warning about the risk for osteoporosis. The relationship between bone health and polycystic ovarian syndrome [PCOS] is debated, but premenopausal women with PCOS are generally not hypoestrogenemic and thus probably not at increased risk for osteoporosis *[D]*.

No fracture data exist regarding HRT use in glucocorticoid-induced osteoporosis, although in small studies it does seem to have significant beneficial effect on lumbar BMD *[A]*. Nonetheless, because glucocorticoids affect steroid sex hormone production, HRT may be reasonable therapy for glucocorticoid-induced osteoporosis in women *[D]*.

Calcitonin. Calcitonin is a polypeptide hormone that inhibits osteoclast mediated bone resorption.

Calcitonin stabilizes or even increases spinal BMD early and late after menopause *[A]*. Only one randomized, controlled trial of calcitonin in postmenopausal women, the Prevention of Recurrence of Osteoporotic Fractures [PROOF] study, has been of sufficient size (n=1255), to demonstrate reduction in vertebral fracture risk *[A]*. There are insufficient data to draw conclusions about nonvertebral fractures.

Calcitonin significantly preserves lumbar bone in glucocorticoid use *[A]*, although no benefit for femoral neck BMD has consistently been demonstrated. A Cochrane review found a nonsignificant trend to fracture reduction in the setting of steroid use (calcitonin vs. placebo, vertebral fracture RR 0.71 [95%CI, 0.26-1.89], nonvertebral fracture RR 0.52 [95%CI 0.14-1.96]).

Calcitonin, in small studies, has been found to significantly reduce the pain of acute vertebral fractures *[A]*.

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. We have not discussed promising therapies that are not available in the United States, for example sodium fluoride and parathyroid hormone.

Combined estrogen and bisphosphonate therapy. This combination may provide additional benefit above either alone. Although both are antiresorptive agents that affect osteoclasts, their exact mechanisms of action are somewhat different. The combination produces significant increases in lumbar and hip BMD compared to placebo or either alone *[A]*. One small study found trend toward reduction in vertebral fracture rates *[B]*.

Calcitriol. This drug is a synthetic form of the active vitamin D metabolite (1,25-dihydroxy-vitamin D) and has FDA approval for management of hypocalcemia and metabolic bone disease associated with end stage renal disease. It is effective in reducing incidence of vertebral deformity *[A]*. Side effects of calcitriol or high doses of other forms of vitamin D include hypercalcemia, hypercalciuria, and nephrolithiasis, and therefore serum and urinary calcium levels must monitored by a subspecialist or others familiar with their use.

Tamoxifen. In postmenopausal women tamoxifen has a small positive effect on BMD of the hip *[B]* and spine *[A]*. In premenopausal women, however, tamoxifen may cause a significant decrease in BMD due to interference with estrogen *[B]*. No data are available concerning tamoxifen and fracture risk.

Testosterone. Testosterone supplementation improves BMD in men who are taking glucocorticoids and have low serum testosterone *[A]*. Testosterone replacement therapy should be strongly considered for any younger man with definite hypogonadism *[D]*. 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. There are no well controlled studies to support use of pharmacologic doses of testosterone (i.e., greater than 200 mg IM every two weeks or 5 mg daily by patch) 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 and by other mechanisms. Hydrochlorothiazide in doses as low as 12.5 mg per day in normotensive persons provides a modest but significant BMD benefit *[A]*. Although there is evidence associating thiazide use with approximately 30% reduction in hip fracture *[C]*, most authorities at this time do not recommend its use specifically for fracture prevention.

HMG-coA-reductase inhibitors. These agents, commonly referred to as "statins", and may reduce fracture risk by as much as 50% *[C]*. The data so far are, however, from observational studies and may be confounded by factors such as lifestyle and obesity. Nonetheless, there are biologically plausible mechanisms by which statins may affect both bone resorption and rebuilding. Inhibition of HMG-coA-reductase decreases production of mevalonic acid, which is a precursor of cholesterol as well as of various proteins involved in osteoclast function. It also appears that statins increase synthesis of a protein that stimulates osteoblasts.

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 estrogenic and possibly antiestrogenic effects, they are postulated to have benefits for postmenopausal women, perhaps without some of the disadvantages of typical estrogens. Data are inadequate to draw conclusions about the role of these agents in management of risk for osteoporotic fracture. A recent randomized, controlled trial showed no benefit *[A]*.

Duration and Cessation of Pharmacologic Therapy

The optimal duration of therapy for osteoporosis is not yet known. Discontinuing estrogen therapy is associated with accelerated bone loss. Thus, women with osteoporosis who discontinue HRT should be considered for monitoring with DEXA and/or for other anti-osteoporotic therapies. Seven year data on alendronate therapy demonstrate its ongoing safety and effectiveness. However, the effect of bisphosphonates on BMD tends to plateau after a few years of therapy. The long half-life of the bisphosphonates suggests that their effects may persist after discontinuing therapy. Recent data show that patients taking two years of placebo (following 5 years of alendronate therapy) maintained spine BMD but had some reduction of hip BMD.

Non-Pharmacologic Strategies

Exercise. Observational data and clinical trials indicate that weight bearing activities, such as walking but not swimming, reduce loss of bone mass, although effects may wane rapidly when exercise is discontinued. There is no direct evidence that exercise decreases risk for osteoporotic fractures.

Fall prevention measures. Prevention of falls requires attention to the numerous risk factors, including medications, gait, vision, and environment. There is no

direct evidence for benefit of exercise alone in the prevention of falls, although certain balance exercises, such as Tai Chi, may decrease the risk of falling *[C]*.

Hip protectors. Hip protectors are anatomically designed plastic shields or pads worn in side pockets of special underwear. Several randomized trials have shown benefit of such protectors, including a large study of frail elderly at risk for falls, which demonstrated a significant, greater than 40% reduction in hip fractures (~21 vs. 46 hip fractures per 1000 person-years protectors versus controls) *[A]*. Unfortunately, patient discomfort and concern about appearance limit compliance.

Follow Up and When to Repeat DEXA

When deciding if and when to repeat a DEXA scan, consider:

- the patient's clinical risk factors for progression of bone loss and for fracture,
- the results from prior scans,
- whether a repeat DEXA will change management,
- whether a repeat DEXA result may improve compliance with therapy even if it will not change management.

Precision and reproducibility. Serial measurements should, if possible, be made with the same equipment. The precision error of DEXA 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%. For example, in a woman with a 2.0% decrease in BMD by DEXA the 95% confidence interval is -4.8 to +0.8%. 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.

Two years for average loss rate. Because of precision and reproducibility of DEXA scans, at least a two-year interval between scans provides the most meaningful information for persons expected to have an average rate of BMD change. This interval is also supported by an analysis of women that who lost BMD during the first year of treatment with alendronate or raloxifene; these women were likely to gain during continued treatment *[A]*. 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.

More frequently 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 DEXA at intervals of 6-12 months is appropriate *[D]*.

Strategy for Literature Search

The literature search for this project started with the results of a literature 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. We searched subsequent literature. The search was conducted prospectively using the major key words of: *osteoporosis* (or *osteoporosis, postmenopausal*); *osteopenia*; either *hip fractures* or *spinal fractures* with either *osteoporosis* or *osteopenia*; English language; *cost savings, cost and cost analysis; sensitivity and specificity, false negative reactions, false positive reactions, likelihood functions, sensitivity, diagnosis; clinical protocols, physician's practice patterns, algorithms, outcome and process assessment (health care), consensus development conferences, practice guidelines, guideline; clinical trials, clinical trials phase IV, controlled clinical trials, multicenter studies, randomized controlled trials, cohort studies.* Specific searches were performed for (1) *postmenopausal osteoporosis* (1996-99), for (2) *steroids* (1994-99), and for *organ transplantation, transplantation* ((1990-99) with each of the following: *densitometry x-ray, bone density, absorptiometry photon; calcium, calcium carbonate, calcium citrate; Vitamin D; estrogens, progestational hormones, androgens, estrogen replacement therapy; diphosphonates; tamoxifen, piperidines; calcitonin; exercise; accident prevention.* Searches were also performed for *men, male; alternative medicine, isoflavones; alkaline phosphatase, hydroxyproline, osteocalcin, bone marker, bone and bones; osteopenia* (1990-99).

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 clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized clinical 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.

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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Annotated References

Related National Guidelines

National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Osteoporosis Int 1998;8(Suppl 4):S1-S88.

An extremely thorough and thoughtful analysis of literature related to postmenopausal osteoporosis through 1996.

NIH Consensus Development Panel. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285;785-95.

A general overview of osteoporosis in all populations, based on expert panel review of data from 1995-1999.

Anonymous. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis & Rheumatism. 2001;44:1496-1503.

An update of recommendations published by the same group in 1996 regarding management of glucocorticoid-induced osteoporosis. Several other societies of professionals who frequently treat patients glucocorticoids have published similar reviews, but this one is probably the most recent and detailed.

Selected Recent References (since 2002)

Women's Health Initiative, various reports:

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA, Jul 2002; 288: 321 - 333.

The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA, April 14, 2004; 291: 1701 - 1712.

Cauley JA, Robbins J, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: The Women's Health Initiative randomized trial. JAMA, Oct 2003; 290: 1729 - 1738.

In postmenopausal women estrogen combined with progestin or estrogen alone decreases risk for hip and for vertebral fractures, but increases risk for a number of other significant medical conditions, including coronary heart disease, stroke, breast cancer, and venous thromboembolic events.

Bischoff-Ferrari HA, Willett WC, et al. Vitamin D supplementation, a meta-analysis of randomized controlled trials. JAMA. 2005;293:2257-2264

A analysis of vitamin D supplementation in older adults (age ≥ 60, mean ~80). Vitamin D 700-800 IU/day but not 400 IU/day was associated with reduction in risk of hip fracture.

Shea BJ, Adachi JD, Cranney A, Griffith L, et al. Calcium supplementation on bone loss in postmenopausal women. The Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD004526.pub2. DOI: 10.1002/14651858.CD004526.pub2.

A Cochrane Collaboration style analysis of the effects of calcium in postmenopausal women. Fifteen trials with 1806 patients met criteria of RCT, placebo vs. calcium supplement ≥ 400 mg/day and vitamin D supplement, if any, ≤ 400 IU/day). Calcium compared to placebo was associated with a small but significant increase in BMD, a trend toward reduction in vertebral fractures but unclear effect on incidence of non vertebral fractures.