

# Screening for Osteoporosis in Men: A Systematic Review for an American College of Physicians Guideline

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**Background:** Screening for low bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) is the primary way to identify asymptomatic men who might benefit from osteoporosis treatment. Identifying men at risk for low BMD and fracture can help clinicians determine which men should be tested.

**Purpose:** To identify which asymptomatic men should receive DXA BMD testing, this systematic review evaluates 1) risk factors for osteoporotic fracture in men that may be mediated through low BMD and 2) the performance of non-DXA tests in identifying men with low BMD.

**Data Sources:** Studies identified through the MEDLINE database (1990 to July 2007).

**Study Selection:** Articles that assessed risk factors for osteoporotic fracture in men or evaluated a non-DXA screening test against a gold standard of DXA.

**Data Extraction:** Researchers performed independent dual abstractions for each article, determined performance characteristics of screening tests, and assessed the quality of included articles.

**Data Synthesis:** A published meta-analysis of 167 studies evaluating risk factors for low BMD-related fracture in men and women

found high-risk factors to be increased age (>70 years), low body weight (body mass index <20 to 25 kg/m<sup>2</sup>), weight loss (>10%), physical inactivity, prolonged corticosteroid use, and previous osteoporotic fracture. An additional 102 studies assessing 15 other proposed risk factors were reviewed; most had insufficient evidence in men to draw conclusions. Twenty diagnostic study articles were reviewed. At a T-score threshold of -1.0, calcaneal ultrasonography had a sensitivity of 75% and specificity of 66% for identifying DXA-determined osteoporosis (DXA T-score, -2.5). At a risk score threshold of -1, the Osteoporosis Self-Assessment Screening Tool had a sensitivity of 81% and specificity of 68% to identify DXA-determined osteoporosis.

**Limitation:** Data on other screening tests, including radiography, and bone geometry variables, were sparse.

**Conclusion:** Key risk factors for low BMD-mediated fracture include increased age, low body weight, weight loss, physical inactivity, prolonged corticosteroid use, previous osteoporotic fracture, and androgen deprivation therapy. Non-DXA tests either are too insensitive or have insufficient data to reach conclusions.

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Osteoporosis in men is substantially underdiagnosed and undertreated in the United States and worldwide (1). Looker and colleagues (2), evaluating the Third National Health and Nutrition Examination Survey database in 1997, estimated that between 300 000 and 2 million Americans older than age 50 years have osteoporosis and up to 13 million may have low bone mass. A 60-year-old white man has a 25% lifetime risk for an osteoporotic fracture (3), and the consequences of the fracture can be severe. The 1-year mortality rate in men after hip fracture is twice that in women (1). Diagnostic evaluation and treatment of men at high risk for fracture remains low, despite the prevalence of this condition in men (1, 4).

Dual-energy x-ray absorptiometry (DXA) is the current gold standard test for diagnosing osteoporosis in people without a known osteoporotic fracture. It is, however, an imperfect test, identifying less than one half of the people who progress to have an osteoporotic fracture. For example, in the Rotterdam Study (5), the sensitivity of DXA-determined osteoporosis was only 44% and 21% in identifying elderly women and men, respectively, who subsequently had a nonvertebral fracture. Clearly, factors other than low bone mass are important in identifying patients at elevated risk for osteoporotic fracture. An increased risk for falling may explain why some factors are identified as risk factors for osteoporotic fractures independent of bone mineral density (BMD) (for

example, tricyclic antidepressants) (6). Although imperfect, a strong and graded relationship exists between DXA-determined BMD and future osteoporotic fracture in women and men (7, 8). The Rotterdam Study (7) reported that the incidence of vertebral and hip fracture approximately doubled for every SD decrease in BMD at the lumbar spine and femoral neck, respectively. Furthermore, pharmacologic treatment of men with low DXA-determined BMD has been shown to decrease the risk for subsequent fractures (9).

Some organizations have called for universal screening of older men with DXA testing (5, 10). Although these universal DXA screening strategies would probably increase the diagnosis rate of undetected male osteoporosis, such strategies may not be cost-effective in all men. Schousboe and colleagues (11) recently reported that uni-

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**Table 1. Search Strategy†**

**Database searched; period covered**  
MEDLINE; 1990–2007

**Limiters**  
English  
Human  
Male

**Search strategy**  
osteoporosis[majr] OR osteoporosis[ti]  
AND  
male[tiab] OR men[tiab] OR gender  
AND  
risk factors[majr] OR risk\*[tiab]  
AND  
bone mineral density OR bone\*[ti] OR risk\*[ti] OR fractur\*[ti]  
NOT  
Results of previous searches

**Items retrieved**  
*n* = 540

† We searched MEDLINE to identify published studies on male osteoporosis between 1990 and July 2007.

versal screening would probably be cost-effective only in men age 80 years or older, although this result was sensitive to the cost of treatment. In addition, DXA is not portable, requires a special technician, and is not readily available in many locales (5, 10–13), and efforts to find a non-DXA test that is suitable for widespread use have not succeeded to date.

We conducted a systematic review of the published literature to identify evidence relevant to screening men for osteoporosis. We focused solely on studies concerning the identification of men with risk factors for fracture that may be mediated through low BMD. Recent reviews have summarized the evidence on non-BMD risk factors, including determining who is at increased risk for falls (14) and treatment of persons at elevated risk (15). Our aims were to determine the risk factors for low BMD-mediated osteoporotic fracture in men that could be used to help select patients for BMD testing and whether non-DXA screening tests could be reliably used to diagnose DXA-defined osteoporosis.

## METHODS

### Search Strategy and Study Selection

We searched MEDLINE from 1990 through July 2007 to find articles relevant to risk factors for low BMD and osteoporotic fracture and screening tests for male osteoporosis (Table 1). In addition to our MEDLINE search, we performed reference mining of retrieved articles and previous reviews and solicited articles from experts.

To be included in our review, a study had to measure risk factors for low BMD or osteoporotic fracture in men or compare a non-DXA index screening test with a gold standard reference test in men (DXA or, for calcaneal ultrasonography, fracture occurrence). Eligible risk factors

were judged to be mediated through low BMD on the basis of published literature or expert opinion. Eligible study designs included controlled clinical trials, cohort studies and case series, case-control studies, and systematic reviews or meta-analyses. We excluded case reports, non-systematic reviews, letters to the editor, and other similar publications.

Four trained researchers (working in pairs) reviewed the list of titles and selected articles for further review. They reviewed each retrieved article with a brief screening form that collected data on demographic characteristics, study design, and clinical outcomes.

### Data Abstraction

Two physicians independently abstracted data and resolved differences by repeated review. For studies evaluating the performance of osteoporosis screening tests, a statistician extracted sensitivity, specificity, and their SEs at the relevant quantitative ultrasonography or questionnaire threshold. We calculated the SEs of sensitivity and specificity for studies that did not report them (16). If the sensitivity or specificity was not reported in a study and if they could not be calculated from the given data, we excluded the study from quantitative analysis. We contacted the original authors of some studies to obtain the sample sizes per group needed to perform this calculation.

### Quality Assessment

To evaluate the quality of the included diagnostic studies, we evaluated for potential sources of bias. Our quality appraisal included components from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) evaluation tool (17) and additional quality variables noted as important in other published studies (11). The QUADAS tool is a 14-item questionnaire that evaluates the bias, data variability, and quality of reporting in diagnostic accuracy studies (18).

### Data Synthesis

For studies of risk factors for low BMD-mediated osteoporotic fracture, we identified a meta-analysis and summarized the results. We assessed the study by using the Overview Quality Assessment Questionnaire (19) and judged it to be of sufficiently high quality and acceptable to use the results. We summarized studies published after this meta-analysis and presented them narratively. For studies of non-DXA screening tests that met inclusion criteria and were clinically appropriate, we reviewed test thresholds for determining osteoporosis across studies to see whether they were comparable and evaluate whether statistical pooling was appropriate. This analysis revealed these studies to be too heterogeneous for statistical pooling. Therefore, where data were available, we abstracted information on the sensitivity and specificity of the screening tests and graphed the data points of studies evaluating the same screening method on receiver-operating characteristic (ROC) curves (20).

### Rating the Body of Evidence

We assessed the overall quality of evidence for outcomes by using a method developed by the Grading of Recommendations, Assessment, Development, and Evaluation group (GRADE) (21), which classifies the grade of evidence across outcomes (Table 2).

### Role of the Funding Source

The U.S. Department of Veterans Affairs Health Services Research and Development Evidence Synthesis Activity Pilot Program provided funding. The funding source was involved in development of the key questions and provided review on a draft version of the evidence report, but it had no role in the decision to submit the manuscript for publication.

## RESULTS

### Literature Flow

Our initial literature search identified 614 titles (Figure 1): 540 from the electronic search, 69 from reference mining, and 5 from content experts. Of these, 177 assessed risk factors for low BMD-mediated osteoporotic fracture and 20 evaluated screening tools for osteoporosis. The studies that addressed screening tools for osteoporosis enrolled a total of 28 359 participants (22–48). Table 3 shows details of these screening studies.

### Risk Factors for Low BMD-Mediated Fracture

We identified a systematic review and meta-analysis by Espallargues and colleagues (49) of risk factors for low BMD-mediated osteoporotic fracture to guide bone densitometry assessments. Espallargues and colleagues searched several databases up to 1997 and identified 94 cohort studies, 72 case-control studies, and 1 randomized clinical trial. Most studies were performed in participants older than age 50 years and used American or European study populations. Where feasible, the authors used fixed-effects methods to provide meta-analytic pooled estimates of risk. They classified risk factors into the following groups: high risk, an associated relative risk or odds ratio of 2 or greater; moderate risk, risk values of between 1.0 and 2.0; no risk, risk values close or equal to the null value, or even a protective effect; and unclassifiable, data were insufficient to reach a conclusion or contradictory.

Strengths of this review include the search strategy and identification of a very large number of articles, categorization of risk factors, and use of meta-analytic techniques to provide summary results. The main limitation is that data specific for men are not presented. The authors performed separate analyses for men and women, found no important differences, and presented results for both sexes combined. The most important high-risk factors relevant to men are age older than 70 years and low body weight (body mass index <20 to 25 m/kg<sup>2</sup>). Additional important high-risk factors are physical inactivity, corticosteroid use, and previous osteoporotic fracture.

Table 2. GRADE Categories of Quality of Evidence\*

GRADE Quality of Evidence	Comment
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

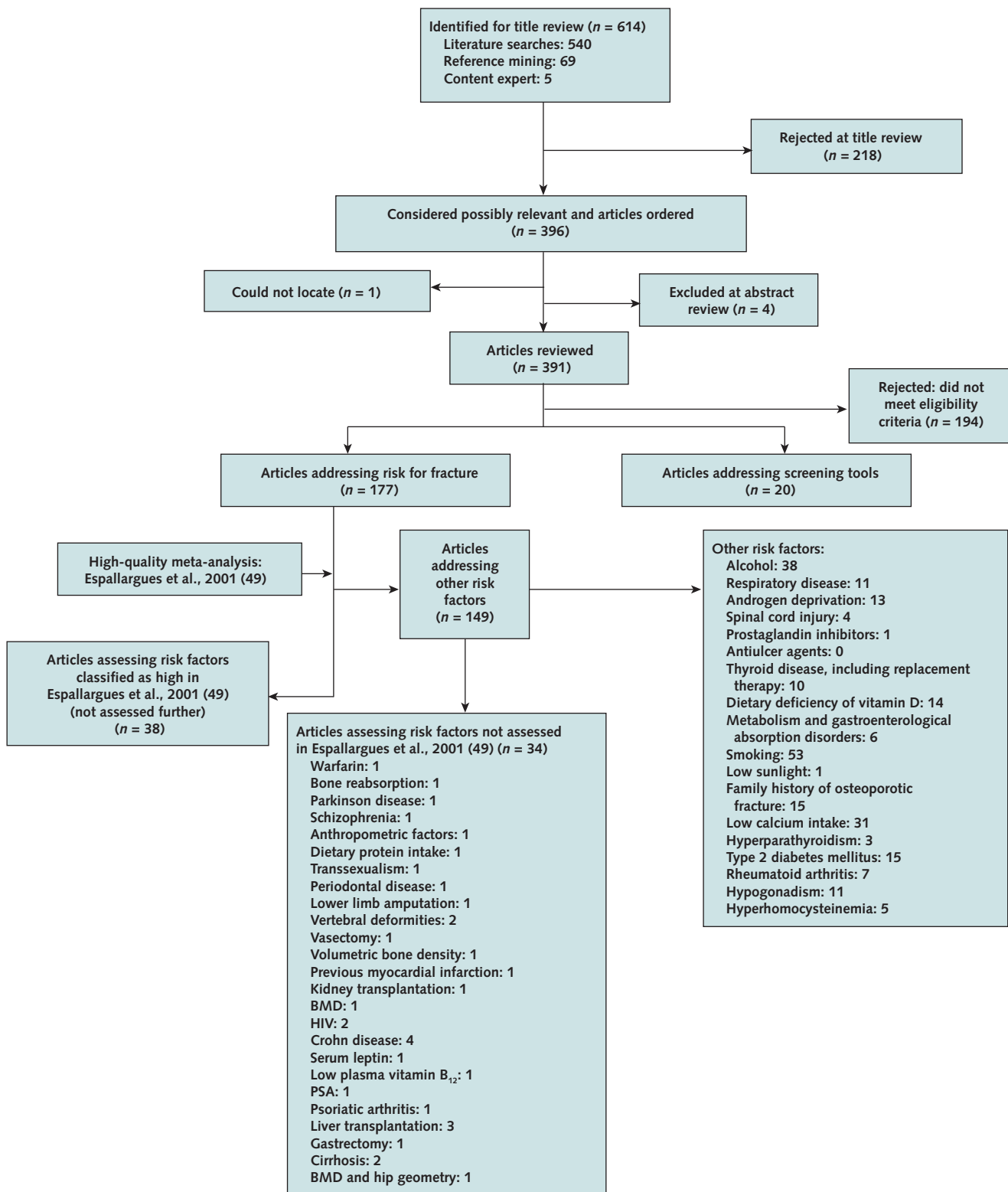
\* GRADE = Grading of Recommendations, Assessment, Development, and Evaluation.

Of the remaining 177 articles we identified, 38 articles evaluated variables that Espallargues and colleagues found to have sufficient evidence to conclude they were high-risk factors. We did not assess these articles further. One hundred five articles assessed risk factors that Espallargues and colleagues called moderate or unclassifiable because of insufficient or contradictory information, and these articles were the target of our continued investigation. We excluded risk factors with only 1 identified study and also excluded hyperhomocysteinemia, a condition of sufficiently rare prevalence in the United States that its use in evaluating men for BMD screening was negligible. Finally, we identified 34 articles assessing factors that were not considered in Espallargues and colleagues' meta-analysis (Figure 1). Not enough articles for any of these factors were available to warrant a synthesis.

We did not assess in detail the 53 studies on cigarette smoking and osteoporosis or fracture in men. A meta-analysis strongly supported an association between cigarette smoking and BMD loss or hip fracture in postmenopausal women; data in men were limited but suggested a similar effect (50). Prospective cohort studies consistently support an association between cigarette smoking and BMD loss in men (51–54), although associations of cigarette smoking with fracture are more variable (3, 55, 56). As a result, we judge that data are sufficient to conclude that cigarette smoking is a risk factor for low BMD and possibly also for osteoporotic fractures, although cigarette smoking is not as strong a predictor as the high-risk factors, on the basis of both the magnitude of the risk and the consistency of the association.

We identified 39 studies assessing the relationship between calcium and vitamin D (31 and 14 studies, respectively) and low bone mass or fracture. We did not assess these further because we are not aware of any validated methods for determining dietary intake of calcium or vitamin D that are feasible for office-based primary care practice. Although some studies report an association between low dietary calcium intake and low bone mass (54, 57), the relationship is not consistently found (53, 58). Furthermore, in a meta-analysis of data from 6 prospective cohorts

Figure 1. Study flow diagram.



Some articles assessed multiple risk factors. A total of 614 titles were identified for review; 20 articles evaluated male osteoporosis screening tools and were included in the analysis. BMD = bone mineral density; PSA = prostate-specific antigen.

encompassing more than 12 000 men, the screening method most feasible for primary care—self-report of daily milk intake—was not associated with an increased risk for osteoporotic fracture (59). Of the studies evaluating vitamin D, 10 were cross-sectional in condition-specific populations (60–62) or more general populations (63–69).

We identified 15 studies assessing a family history of osteoporosis or fracture and low bone mass or fracture. Six studies could not be used because they did not have an appropriate comparison group (67), used ultrasonography rather than DXA as a measure of low bone mass (70), used DXA-determined low bone mass in families rather than a family history of osteoporosis or fracture (71, 72), had no statistical testing (73), or had too few data points to reach a meaningful conclusion (74). One case–control study found that maternal history of hip fracture was associated with existing vertebral deformities (adjusted odds ratio, 1.3 [95% CI, 1.0 to 1.8]) (75). The remaining 8 studies were all cross-sectional in design, and all assessed low BMD, rather than fracture, as the outcome (54, 58, 64, 66, 76–79). Family history was variably defined among studies, for example, as osteoporosis or lost height with age or as history of fractures (or specific fractures, such as hip). The studies were evenly divided between those reporting statistically significant or insignificant association of family history and low BMD. However, the 2 largest studies, both of U.S. populations, assessed 1477 and 5995 men each and reported significant associations (66, 76).

Regarding alcohol use, we identified 3 cohort (55, 80, 81), 3 case–control (56, 82, 83), and 3 cross-sectional (3, 84, 85) studies that assessed self-reported alcohol use as a risk factor for osteoporotic fracture. We also identified 3 cohort (52–54), 1 case–control (86), and 11 cross-sectional (53, 58, 64, 66, 72, 78, 79, 87–90) studies that assessed alcohol as a risk factor for decreased BMD. Two pooled analyses of large prospective cohorts of men found very similar results with respect to osteoporotic fractures: relative risks of about 2.0 with alcohol use of 3 or 4 drinks per day, with increasing relative risks with higher daily alcohol intake (80, 81). The only prospective cohort study that did not find an association with alcohol use and osteoporotic fractures assessed vertebral fractures only (55). In contrast, the studies do not support an association between alcohol intake and a decrease in BMD. In fact, alcohol use was associated with an increase in hip BMD in 2 studies. From this, we conclude that any effect of self-reported alcohol use on BMD is likely to be small.

We identified 8 cohort (57, 62, 91–96) and 5 case–control (97–101) studies specifically evaluating the effects of androgen deprivation therapy (castration or therapy with gonadotropin-releasing hormone agonists) and risk for loss of BMD and fracture. All studies reported a significant association between androgen deprivation therapy for prostate cancer and risk for low BMD and/or osteoporotic fracture. The largest study was an analysis of 50 613 men in the Surveillance, Epidemiology, and End Results pro-

gram with a prostate cancer diagnosis between 1992 and 1997 (91). Men who received androgen deprivation therapy had a statistically significant increased risk for osteoporotic fracture, in a dose-dependent manner. Men who received 9 or more doses of gonadotropin-releasing hormone agonist or had orchiectomy had relative risks of 1.45 and 1.54, respectively (91). Of interest, results varied in 11 other studies assessing the relationship between hypogonadism (variably defined) and osteoporosis or fracture, although many studies had too few patients to draw conclusions (58, 65, 67, 83, 102–105). The strongest evidence came from 3 case–control studies that assessed serum values of testosterone or luteinizing hormone and reported significant associations with osteoporosis (106, 107) or fracture (85). Hypogonadism, defined as a past medical history item, was assessed in only 2 studies—neither of which reported an association but had too few patients to draw conclusions (58, 105).

We identified 15 studies assessing type 2 diabetes and osteoporosis or fracture. Four case–control studies reported mixed results, with most reporting no association (74, 83, 90, 105). Ten cross-sectional studies found mostly no association or an increase in BMD in men with type 2 diabetes (45, 58, 66, 72, 82, 87, 88, 108–110). The only cohort study assessed 998 older male participants (111). The presence of diabetes was assessed by self-report and a fasting blood glucose level (using a follow-up 2-hour oral glucose tolerance test in selected participants). In multivariate models adjusted for age, baseline BMD, weight change, smoking status, renal status, and other variables, the presence of diabetes was not associated with femoral neck or total hip BMD in men at 4 years (111).

We identified 10 studies that assessed thyroid disease or replacement therapy as a risk factor. One study compared hip fracture in men and women and did not include men without hip fracture (112). Four studies were cross-sectional (58, 65, 66, 113). Four were case–control studies: 2 assessed fractures of the distal forearm in mixed populations of men and women in the United States (83) and Sweden (74), 1 assessed osteoporotic vertebral fractures in men in France (105), and 1 assessed hip fracture risk factors in Southeast Asia (82). None of the 8 cross-sectional and case–control studies reported thyroid disease or the use of thyroid medications as a statistically significant risk factor, although many studies had too few patients with any of these risk factors to draw conclusions. The only prospective cohort study followed 5876 men (mean age, 74 years) for an average of 4.1 years. A history of low thyroid hormone as a medical condition and the use of thyroid hormone medication were associated with a statistically significant increased risk for subsequent fracture in univariate analyses but not in multivariate analysis (6). We identified 12 studies that assessed respiratory disease as a risk factor. There were no prospective cohort studies. We identified 2 case–control studies, but they compared hip fracture between men and women and did not include men without

**Table 3. Characteristics of Non–Dual-Energy X-Ray Absorptiometry Osteoporosis Screening Tests\***

Author, Year (Reference)	Location	Sample Characteristics	Men, <i>n</i>	Index Test	
				Test	Site
<b>Index test: bone structural parameters</b>					
Melton et al., 2005 (37)	United States/Canada	Unselected	348	Bone structural parameters	Femur
<b>Index test: questionnaires</b>					
Adler et al., 2003 (23)	United States/Canada	Pulmonary clinic, Asian, veteran	107	24-item questionnaire	NA
Adler et al., 2003 (24)	United States/Canada	Pulmonary and rheumatology clinic, veteran	181	OST (age, weight)	NA
Kung et al., 2005 (34)	Asia	Elderly, Asian	776	OST (age, weight)	NA
Li-Yu et al., 2005 (35)	Asia	Unselected, Filipino	132	OST (age, weight)	NA
Lynn et al., 2005 (36)	Asia	Elderly, Asian	2000	MOST (age, QUI)	NA
<b>Index test: US</b>					
Adler et al., 2001 (22)	United States/Canada	Referred for DXA, veteran	185	US BUA, QUI	Calcaneus
Adler et al., 2003 (23)	United States/Canada	Pulmonary clinic, Asian, veteran	107	US BUA, SOS, QUI	Calcaneus
Grapp et al., 2001 (29)	Western Europe	Referred for BMD	501	US QUS	Calcaneus
Gudmundsdottir et al., 2005 (30)	Scandinavia	Unselected	589	US BUA, SOS, SI	Calcaneus
Kung et al., 2005 (34)	Asia	Elderly, Asian	776	US BUA, SOS, QUI	Calcaneus
Lynn et al., 2005 (36)	Asia	Elderly, Asian	2000	US QUI	NA

\* The table is ordered by reference standard (central DXA, previous fractures) and then by study test (in alphabetical order). AUC = area under the curve; AVU = apparent velocity of ultrasound; BMD = bone mineral density; BMI = body mass index; BUA = broadband ultrasound attenuation; DXA = dual-energy x-ray absorptiometry; MOST = Male Osteoporosis Screening Test; NA = not available; NR = not reported; OR = odds ratio; OST = Osteoporosis Self-Assessment Screening Tool; DXA = dual energy x-ray absorptiometry; QUI = quantitative ultrasound index; QUS = quantitative ultrasonography; RH = rate of hip; Sens = sensitivity; SI = stiffness index; SOS = speed of sound; Spec = specificity; US = ultrasonography.

Table 3—Continued

Reference Test		Results	Included in Quantitative Analysis
Test	Site		
Central DXA	Femur	BMD and structural parameters strongly correlated. For moderate-trauma fractures, best model included age (OR per decade, 1.5), femoral neck section modulus (OR, 1.6), and intertrochanteric buckling ratio (OR, 1.6) (all $P < 0.05$ ).	No
Central DXA	Spine, femur	Best-fit model of questionnaire (to predict hip BMD) included body weight, heel BMD, prednisone use for >7 days, and race, although only BMI and age performed similarly.	No
Central DXA	Spine, femur	Central DXA T-score <−2.0 OST score <1: Sens = 0.62, Spec = 0.89 OST score <2: Sens = 0.69, Spec = 0.82 OST score <3: Sens = 0.74, Spec = 0.72 Central DXA T-score <−2.5 OST score <1: Sens = 0.75, Spec = 0.80 OST score <2: Sens = 0.82, Spec = 0.74 OST score <3: Sens = 0.93, Spec = 0.66	Yes
Central DXA	Spine, femur	Femoral neck BMD T-score ≤−2.5 OST score ≤−1.0: Sens = 0.71, Spec = 0.68	Yes
Central DXA	Femur	Femoral neck BMD T-score ≤−2.5 OST score <−1.0: Sens = 0.91, Spec = 0.66	Yes
Central DXA	Spine, femur	Central BMD T-score <−2.5 MOST score >3: Sens = 0.94, Spec = 0.46	Yes
Central DXA	Spine, femur	Central DXA T-score <−1.5 Heel T-score <0: Sens = 0.89, Spec = 0.40 Heel T-score <−0.5: Sens = 0.79, Spec = 0.48 Heel T-score <−1.0: Sens = 0.65, Spec = 0.75 Heel T-score <−1.5: Sens = 0.49, Spec = 0.84 Heel T-score <−2.0: Sens = 0.30, Spec = 0.94 Heel T-score <−2.5: Sens = 0.07, Spec = 0.98 Central DXA T-score <−2.0 Heel T-score <0: Sens = 0.92, Spec = 0.35 Heel T-score <−0.5: Sens = 0.86, Spec = 0.47 Heel T-score <−1.0: Sens = 0.71, Spec = 0.68 Heel T-score <−1.5: Sens = 0.53, Spec = 0.79 Heel T-score <−2.0: Sens = 0.30, Spec = 0.89 Heel T-score <−2.5: Sens = 0.06, Spec = 0.97 Central DXA T-score <−2.5 Heel T-score <0: Sens = 0.91, Spec = 0.27 Heel T-score <−0.5: Sens = 0.86, Spec = 0.38 Heel T-score <−1.0: Sens = 0.74, Spec = 0.59 Heel T-score <−1.5: Sens = 0.60, Spec = 0.73 Heel T-score <−2.0: Sens = 0.34, Spec = 0.86 Heel T-score <−2.5: Sens = 0.07, Spec = 0.97	Yes
Central DXA	Spine, femur	Central DXA T-score <−2.0 Heel T-score <−1.5: Sens = 0.41, Spec = 0.77	Yes
Central DXA	Spine, femur	Insufficient statistics for sensitivity and specificity calculation	No
Central DXA	Spine, femur	Total hip DXA T-score <−2.5 QUS T-score <0: Sens = 1.0, Spec = 0.14 QUS T-score <−0.5: Sens = 0.86, Spec = 0.28 QUS T-score <−1.0: Sens = 0.82, Spec = 0.49 Femoral neck BMD T-score ≤−2.5 QUS T-score <0: Sens = 1.0, Spec = 0.13 QUS T-score <−0.5: Sens = 0.92, Spec = 0.28 QUS T-score <−1.0: Sens = 0.83, Spec = 0.47	Yes
Central DXA	Spine, femur	Femoral neck BMD T-score ≤−2.5 QUI T-score <−1.2: Sens = 0.76, Spec = 0.72	Yes
Central DXA	Spine, femur	QUI associated with osteoporosis (OR for osteoporosis per 10-point decrement in QUI, 1.71 [95% CI, 1.51–1.93])	No

Continued on following page

hip fracture (112). The other case-control study compared 51 patients with osteoporotic vertebral fractures with 26 patients hospitalized for sciatica or lumbar pain, matched

only by age. In that study, respiratory insufficiency occurred too infrequently to reach any conclusion (105). The remaining studies were cross-sectional in design and as-

Table 3. Continued

Author, Year (Reference)	Location	Sample Characteristics	Men, n	Index Test	
				Test	Site
Mulleman et al., 2002 (39)	Western Europe	Referral	102	US BUA, SOS, SI	Calcaneus
Shin et al., 2005 (43)	Asia	Unselected, elderly, Asian	1225	US BUA, SOS, stiffness	Calcaneus
Bauer et al., 2004 (48)	United States/Canada	Elderly	5608	US BUA	Femur, calcaneus
Donaldson et al., 1999 (27)	Western Europe	Elderly	817	US BUA	Calcaneus
Gonnelli et al., 2005 (28)	Western Europe	Bone clinic	407	US BUA, SOS	Spine, femur, calcaneus
Montagnani et al., 2001 (38)	Western Europe	Unselected	182	US	Spine, femur, finger
Mulleman et al., 2002 (39)	Western Europe	Referral	102	US BUA, SOS, SI	Calcaneus
Rothenberg et al., 2004 (42)	United States/Canada	Unselected	301	US BMD	Calcaneus
Stewart et al., 1995 (44)	Western Europe	Unselected	247	US BUA	Spine, femur, calcaneus
Travers-Gustafson et al., 1995 (45)	United States/Canada	Elderly	529	Peripheral BMD, other, AVU	Radius, patella
Varenna et al., 2005 (46)	Western Europe	Unselected	4832	US BUA, SOS, SI	Calcaneus
Welch et al., 2004 (47)	Western Europe	Unselected	6860	US BUA	Calcaneus

sessed pulmonary patient populations (asthma, chronic obstructive pulmonary disease, or attendees at a pulmonary clinic) (23, 60, 103, 114, 115) or general populations (58, 66, 87, 106, 116). Results from these 9 studies were mixed.

We identified 6 studies that assessed various gastrointestinal and metabolic malabsorption disorders. There were no prospective cohort studies. Five of the studies were cross-sectional and examined various possible risk factors, such as lactose or other malabsorption (65), “intestinal malabsorption” (117), celiac disease (61), “malabsorption syndromes” (82), and receipt of home parenteral nutrition (118). Results were mixed. One case–control study compared 496 patients with a distal forearm fracture with con-

trol participants matched by age and sex. Gastric resection, small- or large-bowel restriction, malabsorption syndrome, or pernicious anemia occurred too infrequently in case patients and control participants to allow any conclusions to be drawn (83).

We identified 4 relevant studies of osteoporosis in patients with spinal cord injury: 1 case–control study and 3 cross-sectional studies (119–122). The case–control study compared 17 male patients with spinal cord injury between 17 and 52 years of age who were matched by age, height, weight, and time spent in physical activity with able-bodied male control participants. Many of the participants were elite sportsmen (119). Eleven of the patients with

Table 3—Continued

Reference Test		Results	Included in Quantitative Analysis
Test	Site		
Central DXA	Spine, femur	QUS is associated with low-trauma fracture (ORs, 2.3 and 2.1 for SOS and SI, respectively), although sensitivity is less than when results are compared with BMD at the lumbar spine (OR, 2.8) and hip (OR, 3.4) with an AUC for BMD of lumbar spine and BUA of 0.80 and 0.69, respectively ( $P < 0.05$ ). Lumbar spine DXA T-score $\leq -2.5$ QUS T-score $\leq -2.5$ : Sens = 0.56, Spec = 0.84 Femoral neck DXA T-score $\leq -2.5$ QUS T-score $\leq -2.5$ : Sens = 0.64, Spec = 0.74 Hip DXA T-score $\leq -2.5$ QUS T-score $\leq -2.5$ : Sens = 0.41, Spec = 0.93 Stiffness index DXA T-score $\leq -2.5$ QUS T-score $\leq -2.5$ : Sens = 0.60, Spec = 0.78	Yes
Peripheral DXA	Radius, calcaneus	Correlations between QUS and BMD were 0.41 to 0.73 in men, with peak mean values for QUS occurring in men age 20–29 years.	No
Fracture occurrence	Femur	Each SD decrease in calcaneal US BUA was associated with an increased rate of hip (RH, 1.97 [CI, 1.32–3.54]) and nonspinal (RH, 1.65 [CI, 1.38–1.96]) fracture. US predicted hip and nonspinal fractures almost as well as it predicted femoral BMD, and the combination of these tests was not better than either test alone.	No
Fracture occurrence	NR	No significant difference between fixed or anatomic BUA values in men with or without a past fracture.	No
Fracture occurrence	Spine, femur, radius, pelvis	Hip BMD (OR, 3.4 [CI, 2.5–4.8]) and QUS stiffness (OR, 3.2 [CI, 2.3–4.5]) had strong associations with fractures and that combining these 2 variables resulted in an even stronger association (OR, 6.1 [CI, 2.6–14.3]).	No
Fracture occurrence	NR	Evaluated usefulness of US of the phalanx; in regression analysis, only 1 variable, bone transmission time, was comparable to DXA variables in determining fracture risk.	No
Fracture occurrence		QUS is associated with low-trauma fracture (ORs, 2.3 and 2.1 for SOS and SI, respectively), although sensitivity is less than when results are compared with BMD at the lumbar spine (OR, 2.8) and hip (OR, 3.4) with an AUC for BMD of lumbar spine and BUA of 0.80 and 0.69, respectively ( $P < 0.05$ ).	No
Fracture occurrence	Spine, femur, radius, shoulder, ribs	Estimated that the Hologic T-score of $-0.2$ corresponds to a BMD of $0.57 \text{ g/cm}^2$ , which corresponds to an increase in relative risk for fracture of 1.4.	No
Fracture occurrence	Spine	No statistically significant relationship between BUA or DXA at any site and fractures in men in bivariate analyses.	No
Fracture occurrence	NR	AVU is highly associated with low-trauma fractures in both women (OR, 1.46 [CI, 1.18–1.81]) and men (OR, 1.69 [CI, 1.24–2.32]).	No
Fracture occurrence	Femur, nonspine	Each SD reduction in QUS measurement resulted in a significant, approximately double increase in risk for hip fracture, independent of age and other clinical variables, consistent with findings in elderly women.	No
Fracture occurrence	Spine, femur, radius	Sex differences in relationship between osteoporosis risk factors and BUA. Age, weight, and height explained 27% of the variance of BUA in women, but only 3% in men.	No

spinal cord injury were tetraplegic and 6 were paraplegic. Bone mineral density by DXA was measured for the total body, arms, legs, left hip, and lumbar spine. Mean T-scores of the legs and hip significantly differed between the spinal cord injury and control groups. Mean T-scores in the patients with spinal cord injury were consistent with osteoporosis in the legs and trochanter and osteopenia in the femoral neck and the Ward triangle. Further supporting the association between spinal cord injury and bone loss were the 3 cross-sectional studies, which reported statistically significant associations among spinal cord injury, bone loss, and/or presence of fracture (120–122). Notable among these was a study of 41 Turkish patients with spinal

cord injury, 32 of whom were male and with a mean age of 34.4 years (121). Bone mineral density  $z$  scores were significantly higher in the upper extremities for paraplegic patients than for tetraplegic patients. When evaluating paraplegic patients alone, the study found that BMD  $z$  scores were significantly higher in the upper extremities than in the lower extremities. This study also demonstrated that BMD  $z$  scores were significantly higher in patients with spinal cord injury and incomplete injuries than in those with complete injuries, in those with spastic paralysis than in those with flaccid paralysis, and in those with a shorter duration of injury. As opposed to cross-sectional studies of other risk factors, this study provides a stronger

Table 4. Summary of Quality of Evidence\*

Topic	GRADE Quality of Evidence
<b>Risk factors for low BMD and osteoporotic fracture</b>	
Strong predictors of an increased risk for low bone mass and osteoporotic fracture in men include increased age (>70 years), low body weight (BMI <20–25 kg/m <sup>2</sup> ), weight loss (>10% from baseline), physical inactivity, and previous osteoporotic fracture.	High
Prolonged systemic corticosteroid therapy and androgen deprivation therapy (in the context of prostate cancer treatment) are strong or moderate predictors of an increased risk for low bone mass and osteoporotic fracture in men.	Moderate
Cigarette smoking is a moderate predictor of an increased risk for low bone mass. Although less established, cigarette smoking is likely to also be a risk factor for fracture.	Moderate for BMD; low for fracture
Spinal cord injury is a moderate predictor of an increased risk for low bone mass and osteoporotic fracture in men.	Low
Alcohol use is probably associated with an increase in osteoporotic fractures, but it is not clearly associated with an increase in osteoporosis as measured by BMD.	Moderate for fracture; very low for BMD
<b>Non-DXA screening tests</b>	
No evidence suggests that calcaneal ultrasonography performs differently in men than in women.	Moderate
Although calcaneal ultrasonography does not seem to be a particularly good test at diagnosing DXA-determined osteoporosis, it appears to be an independent predictor of fractures in men.	Moderate
The OST seems to have comparable test characteristics as calcaneal ultrasonography in diagnosing DXA-determined osteoporosis.	Low

\* BMD = bone mineral density; BMI = body mass index; DXA = dual energy x-ray absorptiometry; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; OST = Osteoporosis Self-Assessment Screening Tool.

level of evidence because patients can act as their own “control,” with BMD measurements above and below the level of injury.

For rheumatoid arthritis, we identified 7 studies. One was a prospective cohort study that assessed bone loss in a sample of 366 patients with rheumatoid arthritis; the effect of rheumatoid arthritis on bone loss could not be determined (123). There were 3 case–control

studies, none of which identified enough men with rheumatoid arthritis to reach any conclusion with 2, 0, and 2 cases each (74, 83, 105). One cross-sectional study found no statistically significant association between rheumatoid arthritis and osteoporosis (66); 1 cross-sectional study reported results for “risk factors” in aggregate and could not determine the risk for rheumatoid arthritis alone (117); and 1 cross-sectional study

Table 5. Quality Assessment of Non–Dual-Energy X-Ray Absorptiometry Osteoporosis Screening Tests

Author, Year (Reference)	Study Design	Male Sample Size at Start/End (Completed), n/n (%)	Representativeness of Study Sample to General Medicine Population	Were Selection Criteria of Study Clearly Described?
Adler et al., 2001 (22)	CCS	185/185 (100)	Unclear	Unclear
Adler et al., 2003 (23)	CCS	107/107 (100)	Yes	Yes
Adler et al., 2003 (24)	CCS	181/181 (100)	Yes	Yes
Bauer et al., 2004 (48)	CCS	5608/5608 (100)	Yes	Yes
De Laet et al., 1998 (26)	CCS	2778/2778 (100)	Yes	Yes
Donaldson et al., 1999 (27)	CCS	817/817 (100)	Yes	Yes
Gonnelli, 2005 (28)	CC	407/407 (100)	No	Yes
Grampp et al., 2001 (29)	CCS	501/501 (100)	No	Yes
Gudmundsdottir et al., 2005 (30)	CCS	589/498 (85)	No	Yes
Kung et al., 2005 (34)	CCS	776/776 (100)	No	Yes
Li-Yu et al., 2005 (35)	CCS	132/132 (100)	No	Yes
Lynn et al., 2005 (36)	CCS	2000/1970 (99)	No	Yes
Montagnani et al., 2001 (38)	CCS	182/182 (100)	Yes	No
Mulleman et al., 2002 (39)	CC	102/102 (100)	No	Yes
Rothenberg et al., 2004 (42)	CCS	301/301 (100)	Yes	Yes
Shin et al., 2005 (43)	CCS	1225/1225 (100)	No	Yes
Stewart et al., 1995 (44)	CCS	247/247 (100)	Yes	Unclear
Travers-Gustafson et al., 1995 (45)	CCS	529/529 (100)	Yes	Yes
Varena et al., 2005 (46)	CCS	4832/4832 (100)	Yes	Yes
Welch et al., 2004 (47)	CCS	6860/6860 (100)	Yes	Yes

\* CC = case–control study; CCS = cohort/case series.

reported a statistically significant association between a history of rheumatoid arthritis and low BMD at the proximal radius, femoral neck, or spine (58).

Three studies assessed hyperparathyroidism. No study had enough patients with hyperparathyroidism to reach conclusions (1, 0, and 2 patients each) (65, 83, 105).

Our estimate of the overall quality of evidence for key risk factors for BMD and osteoporotic fracture by using the GRADE method is found in Table 4.

### Non-DXA Screening Tests

The clinical test characteristics of many non-DXA osteoporosis screening tests have been evaluated in women (124–127). However, little work has been done in men. Whether findings from studies done in women can be applied to men is unclear (128), and there are no consensus guidelines on the use of these tests in assessing and managing osteoporosis in men. This section describes our assessment of the 20 articles we identified concerning alternative screening tests in men.

### Quality Evaluation

Our assessment of the quality of the non-DXA screening test articles showed that most of the 20 included articles met at least most of our quality criteria (Table 5). Only 55% of the studies, however, evaluated populations that were representative of patients who would receive the test in a general screening program—most of the other studies evaluated patients from subspecialty referral clinics.

### Harms of Screening

We did not identify any studies reporting data on harms of screening. Such harms could include false reassurance from false-negative results or anxiety or even inappropriate drug treatment for false-positive results. Additional harms could include time and work loss to get the screening test.

### Screening Test Groupings

Enough data were available to evaluate the performance characteristics of calcaneal ultrasonography and the Osteoporosis Self-Assessment Screening Tool (OST) in diagnosing DXA-defined osteoporosis. We did not synthesize data for other screening tests because of the sparse and heterogeneous nature of the data. Because evidence suggests that calcaneal ultrasonography may predict future fracture, we performed a separate analysis to evaluate the literature in this area. In addition, although we identified no studies on the recently released World Health Organization (WHO) fracture risk algorithm that met our screening test inclusion criteria, we provide a narrative review of the literature to date given the likely importance of this algorithm in future fracture risk assessment.

### Performance of Calcaneal Ultrasonography in Diagnosing DXA-Defined Osteoporosis

Calcaneal ultrasonography, in which an ultrasonography probe is placed on either heel, has the advantages of being portable, inexpensive, and radiation-free. Ultra-

Table 5—Continued

Did All or a Random Sample of the Study Sample Receive Verification Using a Reference Standard?	Did Study Sample Receive the Same Reference Test Regardless of Index Test Result?	Was the Period between Index and Reference Test Short Enough to Be Reasonably Sure That the Target Condition Did Not Change?	Were the Index and Reference Tests Interpreted Independently?	Were Withdrawals from the Study Explained?
Yes	Yes	Yes	Unclear	Unclear
No	Yes	Yes	Unclear	Unclear
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Yes	Unclear
Yes	Yes	Yes	Unclear	Yes
No	Unclear	Yes	Unclear	No
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	Yes
Unclear	Yes	Yes	Unclear	No
Yes	Yes	Yes	Unclear	Unclear
Yes	Yes	Yes	Unclear	Unclear
Unclear	Yes	Yes	Unclear	Unclear
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	No
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	Unclear	Yes

sonography measurements are often reported as T-scores (standardized units) of the quantitative ultrasound index. However, there is no commonly accepted threshold for a positive quantitative ultrasound index reading, and our review showed that thresholds from 0 to  $-2.5$  have been used. We did not include many studies in our analysis because they lacked data to calculate the sensitivity and specificity (29, 36, 38). Because of heterogeneity in thresholds, we did not pool results, but we present our calculations of sensitivity and specificity from individual studies in **Figure 2**.

Using a T-score of  $-1.0$ , we found that calcaneal ultrasonography had a sensitivity of 75% and a specificity of 66% to diagnose BMD-determined osteoporosis (central DXA T-score  $< -2.5$ ) (**Figure 2, left**). When the calcaneal ultrasonography threshold was decreased to  $-1.5$ , specificity improved to 78% but sensitivity decreased to 47%. We constructed an ROC curve from 1 study evaluating male veterans (22) (**Figure 2, left**), which varied calcaneal ultrasonography thresholds from  $-1.5$  to  $-2.5$ . Comparing this with a recently reported ROC curve of calcaneal ultrasonography primarily in women (124) showed these curves to be similar, suggesting that calcaneal ultrasonography probably performs comparably in men and women.

#### **Performance of OST in Identifying DXA-Defined Osteoporosis**

The OST, which uses a person's age and weight to develop a risk score ( $[(\text{weight in kilograms} - \text{age in years}) \times 0.2]$ , truncated to an integer) (24), is a simple test that has been evaluated primarily in Asian women (129). More recently, many evaluations have been performed in men, with particular attention to the veteran population (24). As with calcaneal ultrasonography, there is no commonly accepted OST risk score threshold, and thresholds from  $-1$  to 3 have been used (**Table 3**).

Two studies of evaluations of Asian (Chinese and Filipino) men (34, 35) found that at a threshold of  $-1$ , the OST had a sensitivity of 70% to 90% and a specificity of about 70% to diagnose BMD-determined osteoporosis (**Figure 2, right**). In a study of OST in U.S. veterans (24) (**Figure 2, right**), the authors found that at a threshold of 3, the OST had a sensitivity of 93% and a specificity of 66%. Sensitivity decreased to 75% and specificity increased to 80% when the OST threshold was decreased to 1. Of note, at all thresholds evaluated, the OST had higher sensitivity and specificity than calcaneal ultrasonography, although this analysis is limited by lack of available data points.

#### **Calcaneal Ultrasonography and Fracture Risk**

Calcaneal ultrasonography seems to be independently associated with and moderately predictive of fragility fracture in men. One study found that each SD reduction in ultrasonography measurement resulted in an approximate 2-fold increase in hip fractures that was independent of age

and other clinical variables and similar to findings in elderly women (46). Similarly, a study published from the ongoing MrOS (Osteoporotic Fractures in Men) study (130), a large population-based study of older men, found that each SD reduction in calcaneal ultrasonography measurement was associated with an increased risk for hip (relative risk, 2.0 [CI, 1.3 to 3.5]) and nonspine fracture (relative risk, 1.7 [CI, 1.4 to 2.0]). Finally, another study found that ultrasonography stiffness variables had a strong association (odds ratio, 3.2 [CI, 2.3 to 4.5]) with previous fragility fracture (28).

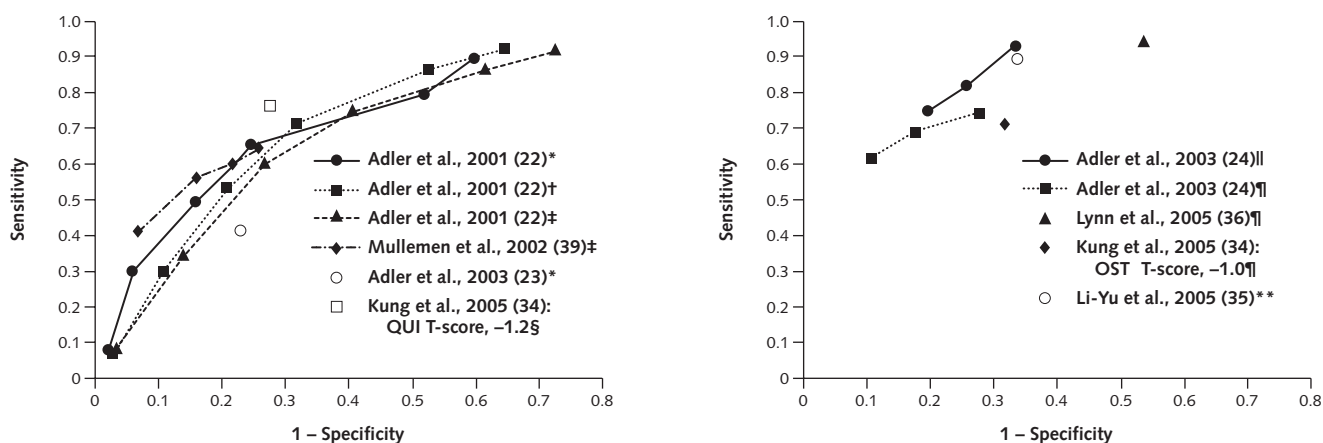
Whether the combination of BMD measurements and calcaneal ultrasonography is better to assess for fractures than either test alone is unclear. One study found that both BMD of the hip (odds ratio, 3.4) and ultrasonography (odds ratio, 3.2) were strongly associated with fragility fracture (28). If BMD and ultrasonography results were combined, the odds ratio for fracture association increased to 6.1. However, an analysis of ROC curves for hip fracture prediction from the MrOS study for ultrasonography alone (area under the ROC curve [AUC], 0.84), BMD alone (AUC, 0.85), and their combination (AUC, 0.85) suggested that the combination was not superior to using either method alone (48). As such, whether an optimal male osteoporosis screening program should include BMD, ultrasonography, or a combination of these 2 or other test methods is unclear.

#### **The WHO Absolute Fracture Risk Algorithm**

Much like the Framingham Risk Score (131), the recently released WHO fracture risk algorithm is a multivariate model that incorporates clinical risk factors to determine a person's absolute risk for an adverse outcome over a set period (for example, absolute risk for fracture over 10 years) (13). Clinical risk factors included in the model are age, sex, previous fracture, femoral neck BMD, body mass index (weight, height), past use of prolonged systemic supraphysiologic glucocorticoids, history of rheumatoid arthritis, parental history of hip fracture, current cigarette smoking, and current alcohol intake (132). A decision to treat is based on whether a person's absolute fracture risk meets a predetermined intervention threshold. These thresholds may be determined by various methods, including cost-effectiveness analyses.

The risk factors used in the WHO algorithm were determined through evaluation of 9 large, prospective, population-based cohorts involving more than 46 000 participants, approximately 15 000 of whom were men (8). Although the algorithm has been reportedly validated in 11 other independent population-based cohorts that involved more than 230 000 participants, fewer than 200 of those (0.03%) were men (8). The WHO risk calculator, called FRAX, is now available online ([www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)).

**Figure 2.** Receiver-operating characteristic curves for calcaneal ultrasonography (left) and the Osteoporosis Self-Assessment Screening Tool (OST) (right) in identifying dual-energy x-ray absorptiometry (DXA)-determined osteoporosis.



The plotted curves were derived from abstracted data of included studies for calcaneal ultrasonography and OST against DXA as the reference standard. QUI = quantitative ultrasound index. \*Threshold for positive test result: central DXA T-score = -1.5. †Threshold for positive test result: central DXA T-score = -2.0. ‡Threshold for positive test result: central DXA T-score = -2.5. §Threshold for positive test result: calcaneal ultrasonography T-score = -1.0. ||Threshold for positive test result: bone mineral density T-score = -2.0. ¶Threshold for positive test result: bone mineral density T-score = -2.5. \*\*Threshold for positive test result: OST score = -1.0.

### Summary

Our estimate of the overall quality of evidence on non-DXA screening tests by using the GRADE method is found in Table 4.

### DISCUSSION

Our review of the literature finds that the most important risk factors for low BMD-mediated osteoporotic fracture in men without a known diagnosis of osteoporosis or fracture are increased age (>70 years) and low body weight (body mass index <20 to 25 kg/m<sup>2</sup>). Additional important risk factors include certain health conditions and medications, particularly weight loss, physical inactivity, corticosteroid use, previous osteoporotic fracture, and androgen deprivation therapy. Cigarette smoking is associated with lower BMD, but there is less evidence in men to determine its association with fracture.

Few published studies have evaluated the clinical performance characteristics of non-DXA osteoporosis screening tests in men. Our analysis of these studies finds that calcaneal ultrasonography may perform similarly in men and women in predicting DXA-determined osteoporosis. In addition, the OST, a simple osteoporosis screening questionnaire involving only 2 variables (age and weight), seems to be at least as sensitive and specific as calcaneal ultrasonography in diagnosing DXA-determined osteoporosis in men. More recently, a similar male osteoporosis screening tool incorporating age, weight, and history of chronic obstructive pulmonary disease accurately predicted men who were at risk for hip fracture (133). The strongest predictor in this model was weight less than 70 kg.

Our evaluation of the performance of calcaneal ultra-

sonography against a reference standard of DXA seemed similar to a recently published ROC curve analysis by Nayak and colleagues (124) on calcaneal ultrasonography that included studies primarily evaluating women. Similar to Nayak and colleagues' findings, we conclude that calcaneal ultrasonography does not seem to be of adequate sensitivity or specificity at commonly used threshold values to identify DXA-determined osteoporosis in men. However, more research is needed to draw definitive conclusions. Although calcaneal ultrasonography does not seem to be particularly good at diagnosing DXA-determined osteoporosis, it appears to be an independent predictor of fractures in men. Calcaneal ultrasonography measurements do identify a population of patients who will have fracture, which is the end point that clinicians and patients are ultimately concerned about. However, because most clinical trials of osteoporosis drugs have recruited patients on the basis of a BMD score and not an ultrasonography score (134–137), whether those identified at risk for fracture by ultrasonography will benefit from current osteoporosis drug therapy is not yet known. This finding is likely to be true for all patients identified to be "at risk" through the non-DXA screening tests evaluated in our review.

The recently released WHO fracture risk algorithm, which focuses on absolute (rather than relative) fracture risk, is based on clinical risk factors for fracture. This algorithm may alter and improve our management of osteoporosis, similar to how the Framingham Risk Score has standardized our evaluation of cardiovascular risk and has enabled determination of thresholds for intervention. Further validation of this algorithm in men is needed.

Our study reflects the limitations of the published

studies. Although we identified many risk factor studies published since the 1997 meta-analysis, heterogeneity precluded us from calculating pooled estimates of relative risk. In addition, our comprehensive review identified only 20 studies evaluating osteoporosis screening tests in men. Only quantitative ultrasonography and the OST had sufficient data to form preliminary conclusions. It remains unclear whether other tests might be useful as screening tests in men.

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