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To cite this article: T. J. de Villiers (2018): Should women be screened for osteoporosis at midlife?, Climacteric, DOI: 10.1080/13697137.2017.1406914

To link to this article: https://doi.org/10.1080/13697137.2017.1406914

Published online: 15 Feb 2018.
Should women be screened for osteoporosis at midlife?

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ABSTRACT

Osteoporosis and associated fractures are common in women after midlife and will increase as the population ages. Osteoporosis-related fractures cause a significant increase in morbidity and mortality. Osteoporosis decreases the quality of life and productivity of many older women, with an increasing burden on health-care resources. Future risk of fracture can be managed by evidence-based interventions. It is thus appropriate to estimate the future risk of fracture in all women at the age of 50 years or at menopause, whichever occurs first. This can be achieved in a non-invasive fashion by targeted clinical history-taking. The future risk of fracture can be quantified using computerized models that integrate all risk factors, with or without dual-energy X-ray absorptiometry (DXA). Individuals found to be at increased risk of fracture need also to be assessed by DXA and, in the absence of lateral vertebral assessment, also by conventional X-ray imaging. All women should be screened by DXA at the age of 65 years, if not done before that time. At the age of 50, all women should be informed about a bone-friendly lifestyle.

Introduction

The purpose of screening is to identify a potentially serious disease at an early stage when intervention can have a positive effect on the outcome of the disease. In terms of osteoporosis, screening implies that individuals at increased risk of fracture be identified and managed in such a way as to prevent fractures.

Screening for osteoporosis is an attractive proposition as osteoporosis-related fractures are indeed a serious clinical outcome with an associated increase in mortality and morbidity. Furthermore, the burden of disease is increasing as the world population is aging. Fortunately, clinical factors correlating with the risk of fracture can be identified by means of targeted clinical history-taking by any health-care provider. Bone strength can be accurately determined in at-risk individuals in a non-invasive fashion by dual-energy X-ray absorptiometry (DXA). Low bone mineral density (BMD) and osteoporosis have been defined using DXA criteria. There are several interventions known that can prevent fractures in at-risk patients. The answer to the question of whether we should screen for osteoporosis is thus affirmative. The question though is who and when and how to screen in the best targeted approach to avoid over-diagnosis, misdiagnosis or creating a false sense of security. We thus require good sensitivity in addition to acceptable specificity.

The disease

Osteoporosis is defined as a systemic skeletal disorder that reduces the strength of bone, resulting in an increased risk of fracture.Fractures can occur as a result of minimal trauma, such as a fall from own body height. The most common osteoporosis-related fractures are fractures of the vertebral. Major non-vertebral osteoporosis-related fractures are fractures of the hip, wrist, sacrum, ribs, sternum, clavicle and humerus. All these fractures are important in terms of disability and pain. Osteoporosis-related fractures result in significant morbidity and increased mortality. Osteoporosis-related fractures are common and will affect at least one-third of women >50 years of age. It is estimated that osteoporosis affects 75 million people in Europe, the USA and Japan, and this is estimated to increase by 240% by 2050. It is estimated that more than 2 million osteoporosis-related fractures occurred in the USA during 2005, at a cost of $19 billion. Hip fractures accounted for 72% of these costs. In 2015, it was estimated that about 12% of the total population of 7.3 billion people were aged 60 years or over. The world population is not only increasing but the percentage of women above the age of 60 years is also rising. This underlines the need to prevent chronic diseases of aging, including osteoporosis.

Clinical risk factors

A targeted clinical history of midlife women can identify the following risk factors for future fractures:

- Advanced age increases the risk of fracture: a BMD T-score (BMD compared to that of a young adult) of –2.5 at 75 years of age implies a greatly increased risk of fracture compared with the same value at 50 years of age.
Fractures in adults are rare before the age of 50 and increase thereafter in correlation with aging. Midlife is thus an appropriate time for screening for the future risk of fracture.

- **Women** have an increased risk of fracture compared with men. After age 50 years, one in three women and but only one in five men will suffer a fragility fracture.
- An **adult T-score** is regarded as the gold standard in the diagnosis of osteoporosis. It was also used in the pivotal trials of all modern bone-specific drugs. DXA results can thus be used as a reasonable predictor of drug response. As a result, the uptake of QUS for screening purposes has remained low and DXA is still regarded as the gold standard.

### Estimation of bone mineral density by DXA

The diagnosis of osteoporosis historically required the presence of a fracture. Bone densitometry by DXA has provided a non-invasive, reliable and reproducible index that is validated as a good risk factor for fracture in the untreated patient without a fracture\(^9\). There is a strong continuous relationship between BMD values and osteoporotic fractures, with a 1.5- to 2.6-fold increase in fracture risk for every standard deviation decrease in BMD, depending on the site of BMD measurement and the site of fracture\(^14\). The operational diagnosis of osteoporosis, as defined by the World Health Organization in 1994, requires a DXA BMD value of 2.5 standard deviations below the peak value for a young Caucasian female (T-score \(-2.5\))\(^15\). DXA is regarded as the gold standard in the diagnosis of osteoporosis. It was also used in the pivotal trials of all modern bone-specific drugs. DXA results can thus be used as a reasonable predictor of drug response. The drawback of DXA is that it is relatively expensive, not mobile and mostly unavailable in remote areas.

### Bone strength estimation by ultrasound

Quantitative ultrasound (QUS) applications offer an alternative means of measuring skeletal health. They have been advocated as alternative means of screening to DXA in view of being less expensive and mobile\(^16\). The calcaneus as a weight-bearing bone is the preferred site for QUS\(^17\). Although a certain degree of correlation has been found between QUS and DXA results in groups of women, the clinical value of a single QUS measurement in an individual remains unclear.

DXA and QUS measure different aspects of bone quality and quantity. QUS-derived T-scores cannot be applied to the same diagnostic cut-offs as used in DXA.

QUS should not be used to start therapy or to monitor response to therapy. As a result, the uptake of QUS for screening purposes has remained low and DXA is still regarded as the gold standard.

### Markers of bone turnover

High bone turnover has been associated with an increased risk of fracture. Various markers of bone turnover can be measured in the serum or urine\(^18\). Biochemical markers are divided into markers of bone resorption (serum C-telopeptide and urinary N-telopeptide) and markers of bone formation (serum bone-specific alkaline phosphatase and osteocalcin). Although these tests are very useful in clinical studies to judge the effect of medication on osteoporosis, markers of bone turnover are not used for diagnosis of osteoporosis and do not improve prediction of bone loss or fracture within an individual. They can thus not be used as a primary screening tool.

### The detection of vertebral fractures

The majority of vertebral fractures are morphometric fractures, which, although asymptomatic, have the same clinical implications as symptomatic fractures. Morphometric fractures are traditionally diagnosed utilizing conventional X-rays. Lateral vertebral assessment by DXA has simplified the detection of asymptomatic vertebral fractures and should be routinely done at the time of DXA examination\(^19\).

### Integrated models of fracture prediction

Several models, based on risk factors for fracture, with or without the addition of DXA-derived BMD values, have been developed. The FRAX\(^20\) fracture risk calculator is the most widely used platform to identify individuals who should undergo further clinical assessment. FRAX\(^20\) can be accessed online at [https://www.sheffield.ac.uk/FRAX/](https://www.sheffield.ac.uk/FRAX/). It was developed based on the placebo arms of large clinical studies with fracture outcomes. It is country-specific and the result is expressed as a 10-year probability of fractures. Differences between FRAX\(^20\) and other calculators such as the Garvan fracture risk calculator have recently been discussed by Kanis and colleagues\(^21\).
Interventions for midlife women identified as at high risk of fracture

Bone-friendly lifestyle changes such as an appropriate diet, exercise, cessation of smoking and heavy drinking, and the avoidance of bone-toxic medication should be advocated to all midlife women. Several medications have been registered for the prevention of fractures and the treatment of osteoporosis. A detailed discussion of these drugs is outside the scope of this paper. These drugs include menopausal hormone therapy, selective estrogen receptor modulators, bisphosphonates, denosumab, teriparatide and abaloparatide.

Present recommendations for the screening of osteoporosis

There is consensus amongst all the major societies that universal screening for fracture risk by non-invasive assessment of risk factors is indicated in all midlife women from the age of 50 years or at menopause and yearly thereafter. There is also agreement that DXA-based screening is indicated after the age of 65 in all women not tested previously. There is also agreement that all women with fractures after age 50 should be further assessed. Indications for DXA-based screening between ages 50 and 65, in women without fracture, are advised on a case-finding strategy based on non-invasive risk factor assessment. The threshold value for the performance of a DXA study between 50 and 65 years based on risk factors is ill defined. The International Menopause Society, the North American Menopause Society, the National Osteoporosis Foundation (US), and the American College of Obstetrics and Gynecology regard the presence of a risk factor(s), in addition to being postmenopausal, as an indication for DXA. The International Osteoporosis Foundation advises that the FRAX risk calculator be used but does not recommend a threshold value. The United States Preventive Services Task Force (USPSTF) recommends DXA screening in women younger than 65 whose fracture risk (based on FRAX) is equal to or greater than that of a 65-year-old White woman who has no additional risk factors. Based on the US FRAX tool, a 65-year-old White woman with no other risk factors has a 9.3% 10-year risk for any osteoporotic fracture. White women between the ages of 50 and 64 years with equivalent or greater 10-year fracture risks based on specific risk factors include but are not limited to the following persons: (1) a 50-year-old current smoker with a BMI less than 21 kg/m², daily alcohol use, and parental fracture history; (2) a 55-year-old woman with a parental fracture history; (3) a 60-year-old woman with a BMI less than 21 kg/m² and daily alcohol use; and (4) a 60-year-old current smoker with daily alcohol use. Although the USPSTF recommends using a 9.3% 10-year fracture risk threshold to screen women aged 50–64 years, clinicians also should consider each patient’s values and preferences and use clinical judgment when discussing screening with women in this age group. Menopausal status is one factor that may affect a decision about screening in this age group.

Conclusion

Osteoporosis and related fractures are common and will be increasing as the world population ages. Osteoporosis is associated with serious mortality and morbidity. The burden of disease places a huge strain on available healthcare resources. Fractures mainly occur from midlife and beyond. It is possible to identify women at risk of fracture and to reduce the risk of fracture by suitable intervention. At the age of 50 or at menopause, all women should be counseled on bone-friendly lifestyle changes and the risk of fracture should be assessed by identifying risk factors by targeted clinical history-taking. In an individual thus identified, including women with a known fracture sustained in adult life, further testing by DXA is advised. All women should have BMD assessed by DXA at age 65, if not previously done.

Conflict of interest The author has acted as a consultant or speaker for Adcock Ingram, Amgen, Aspen, Cipla, Bayer, MERCK and Pfizer.

Source of funding Nil.

References


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