SPECIAL ARTICLE

OSTEOPOROSIS IN CLINICAL PRACTICE — BONE DENSITOMETRY AND FRACTURE RISK

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Osteoporosis is a condition of decreased bone mass and bone density associated with an increase in fracture risk. Bone mineral density (BMD) of the lumbar spine and femur can be reliably measured by double-beam X-ray absorptiometry (DEXA), which provides a measure of bone strength. Reduction in BMD is a continuum and is associated with a progressive increase in fracture risk. The diagnosis of osteoporosis is based on BMD relative to that of healthy young adults and criteria for diagnosis are arbitrary. The original 'normal' BMD data published by some manufacturers were relatively high, leading to a relative over-diagnosis of osteoporosis. Revised normative BMD values of the spine and femur and revised criteria using degrees of severity are proposed and may provide a better basis for diagnosis and for the management of patients with osteoporosis. The indications for BMD measurement, the age at which BMD is measured, and number of measurements, depends upon the purpose of the measurement and how the result will affect the management of each patient in clinical practice.

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Osteoporosis is characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and fracture risk. The lifetime risk of a fracture of the spine, radius or femur due to osteoporosis in a 50-year-old Caucasian woman in the UK or North America is about 15%. The lifetime risk of any fracture due to osteoporosis approaches 40% in women and 13% in men. The risk of fracture is as great as that of having a heart attack and at least four times greater than that of developing breast cancer. Osteoporotic fractures are a major cause of morbidity and mortality and of impaired well-being, especially in the elderly. They are also a major social and economic health problem in terms of numbers of patients affected and the cost of treatment.

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OSTEOPOROSIS AND BONE COMPOSITION AND STRENGTH

Osteoporosis is a bone disorder in which total bone mass is reduced without any change in the ratio of mineralised to non-mineralised bone. This is in contrast to osteomalacia and osteitis fibrosa, where mineralised bone is reduced and replaced by osteoid or fibrous tissue. Osteoporosis and osteomalacia can also be combined, and a definitive diagnosis may only be made on bone biopsy. It is often impossible to distinguish between these conditions using radiography or bone densitometry. The term 'osteopenia' is best reserved for the changes seen on radiograph or bone densitometry, as this does not imply any particular underlying abnormality or cause.

Osteoporosis is a generalised process affecting the whole skeleton, but some bones are more affected and more likely to fracture than others. Bone loss is greater in trabecular bone, which has four times the turnover of cortical bone, and bones with a large proportion of trabecular bone, such as the vertebrae and femoral neck, are more likely to become osteoporotic and to fracture. Bone strength is determined by bone mineral density (BMD), bone architecture and total bone mass. Several methods have been developed for measuring BMD, which accounts for 70 - 80% of the compression and torsion strength of bone *in vitro*.[1] The compressive strength of cancellous bone is proportional to the square of the density, so that small changes in BMD are associated with relatively large changes in bone strength. Reduction of bone density, particularly of trabecular bone, is associated with a breakdown of bone architecture and 'cross-bracing', which is another important factor affecting bone strength. Because BMD is a major determinant of bone strength and can be measured accurately and reliably, the diagnosis of osteoporosis is now based on the measurement of BMD.

However, the risk of a fragility fracture depends not only on bone density and bone strength but also on several other factors including postural instability and propensity to falls, impairment of muscle strength and neuromuscular co-ordination and the risk of trauma and presence of environmental hazards.[2] Many of these factors increase with age and a fracture may be due as much to these and other factors, such as hip geometry,[3] as to loss of bone density and bone strength. Although BMD measurements are now used to define osteoporosis, it is important to remember that BMD is not the only factor determining fracture risk.

BMD IN NORMAL WOMEN AND MEN

Total bone mass and BMD increase throughout childhood and adolescence, reach a peak around 20 years of age, and then normally remain at a plateau until age 40 - 50. The peak bone

mass in men is 10 - 50% higher than in women depending upon the site of measurement, the difference being greater in cortical bone and the appendicular skeleton.[4] From 40 years of age there may be a slow loss of bone of between 0.5% and 1% per year in men and in women until the menopause. After the menopause there is marked acceleration in bone loss to between 2% and 5% per year due to the fall in oestrogen secretion by the ovaries. Accelerated bone loss continues for at least the next 5 - 10 years and may then decline to reach a level of about 0.5% per year by age 75. Bone loss in the early postmenopausal years occurs mainly in cancellous bone and in the axial skeleton, but by age 75 women have lost about the same amount of bone from the axial and appendicular skeleton. BMD is determined by the peak bone mass, the rate of bone loss and the duration of loss (i.e. time since menopause in postmenopausal women). At age 40 - 50 the BMD is primarily a measure of peak bone mass and it provides a guide to the possible development of osteoporosis and to the future risk of fracture, although at this age only 2.5% of women will have a BMD in the osteoporotic range. By age 70, however, BMD is determined equally by peak bone mass and by the amount of bone lost since the menopause, and about 30% of women will have BMD measurements in the osteoporotic range. By 80 years of age 50% of women will have osteoporosis.

BMD — GENETIC AND RACIAL FACTORS

Genetic and racial factors have an important effect on peak bone mass, although the rate of bone loss does not appear to differ significantly between black, Caucasian and Japanese populations.[4] Black women have a higher peak bone mass and higher BMD than Caucasian women, even when adjusted for weight and height, and have a lower incidence of osteoporotic fractures.[5] Twin and family studies suggest that about half of the differences in peak bone mass between different individuals are due to genetic factors and about half to environmental factors. The genetic factors may be related to variability in the inheritance of the vitamin D receptor gene.[6] With advancing age the effect of genetic and other factors that determine peak bone mass becomes less and factors that cause bone loss, such as the menopause, have an increasing effect on the development of osteoporosis.

METHODS OF MEASURING BMD

Several techniques are available for the measurement of BMD and bone mass, including dual energy X-ray absorptiometry (DEXA), quantitative computed tomography (QCT) and quantitative ultrasound (QUS). DEXA has become the method of choice because of its high reproducibility, low radiation dose (less than natural background) and ability to measure BMD at both axial and appendicular sites. It is the only method by which bone density can be measured in both the femur and the vertebrae. This is important because the best predictor of the risk of fracture of any bone is the BMD at the site of measurement,[7] and femoral fractures are by far the greatest cause of morbidity and mortality. DEXA measurements of bone density by skilled operators are very precise, with coefficients of variation of 1% for the spine and 3% for the femur.

QCT has been used to measure the BMD of the lumbar spine and peripheral bones such as the radius, ulna and tibia. It permits separation of the BMD of trabecular and cortical bone of the vertebrae and provides a volumetric measurement of BMD. However, QCT of the spine requires larger doses of radiation and is less precise than DEXA. QCT measurements of the femur are not currently available and QCT has largely been superseded by DEXA in the diagnosis of osteoporosis in most centres. Peripheral QCT requires less radiation and permits separate assessment of density and morphometric changes of peripheral bones.[8]

Ultrasound (US) is a mechanical wave (not a radiation), and its propagation in bone is very complex. The velocity and attenuation of ultrasound is determined not only by the mineral content but also by the structural properties of bone. The speed or velocity of US (SOS) correlates with both the density and the elasticity of bone, while broad-band ultrasound attenuation (BUA) is principally dependent on the structural characteristics of bone. A number of QUS devices have been developed that measure both SOS and BUA, and the manufacturers have derived different combined indices of bone density and structure such as 'stiffness' (Lunar) and 'quantitative ultrasound index' (Hologic). The bone most studied with QUS is the calcaneus. SOS and BUA measurements of the calcaneus correlate with BMD measurements of the calcaneus, femur and lumbar spine (Table I),[9] but the correlation is not sufficiently close to allow prediction of the BMD of the femur and vertebrae in individual subjects. QUS measurements of the calcaneus nevertheless appear to provide an indication of the risk of femoral neck fracture that is independent and as good as that of BMD as measured by DEXA. A decrease of 1 standard deviation (SD) of either QUS or BMD is associated with an approximate doubling of the risk of femoral neck fracture. Combining QUS and BMD measurements may significantly improve the prediction of fracture of the femur.[10] However, QUS indices are only indirectly correlated with BMD and do not permit the diagnosis of osteoporosis according to World Health Organisation (WHO) criteria, which are based on BMD. QUS is

Table I. Correlation coefficients between DEXA and QUS[9]

BMD by DEXA	Calcaneus SOS	Calcaneus BUA
Calcaneus	0.756	0.617
Total body	0.650	0.574
Lumbar spine	0.467	0.447
Femoral neck	0.691	0.663

also not currently applicable to the spine and does not provide a prediction of the vertebral fracture risk. This is a disadvantage as changes in the spine often precede those in the femur. It is therefore unlikely that QUS will replace DEXA in the assessment of fracture risk due to osteoporosis in individual patients. QUS has nevertheless been widely advocated as a screening procedure for the determination and prediction of osteoporosis as QUS machines are simpler, portable and less expensive than DEXA and no radiation is involved.

BMD, FRACTURE RISK AND DIAGNOSIS OF OSTEOPOROSIS

DEXA measurements of BMD are expressed as absolute values (g/cm^2) based on bone mineral content (BMC) divided by the particular area of bone scanned. BMD measurements follow a Gaussian distribution and can be defined in terms of the mean and SD. The SD does not change with age, and the 'normal' range of BMD can be specified either as that applicable to a particular age (Z-score) or as that of healthy young adults (T-score). The risk of fracture is directly related to the absolute BMD irrespective of age, and the diagnosis of osteoporosis is based on the BMD relative to that of healthy young adults or T-score. Normative data are most commonly given for females as osteoporosis is much more common in women. Men have a higher peak bone mass, lose bone less rapidly, and have a lower risk of fracture for any given BMD than women. Different normal ranges and different criteria for the diagnosis of osteoporosis and assessment of fracture risk are therefore required for men.[11]

The risk of a fragility fracture progressively increases with decrease in BMD such that a decrease of 1 SD corresponds to an approximately 1.5 increase in risk of vertebral fracture and a threefold increase in risk of femoral fracture.[7] BMD and risk of fracture are a continuum like blood pressure and blood cholesterol. The relation between BMD and the risk of a fragility fracture is at least as close as that between blood pressure and risk of stroke, and is closer than that between blood cholesterol and the risk of myocardial infarction. BMD measurements in women with a femoral and/or vertebral fracture and in those without fractures, however, overlap, and there is no specific threshold below which fractures suddenly become more frequent. The term 'fracture threshold' is therefore a misnomer and is misleading. The diagnosis of osteoporosis in terms of BMD measurements depends entirely upon the normative data and the diagnostic criteria chosen. Osteoporosis is not a specific disease entity but rather a state of decreased bone density and bone mass relative to that of healthy young adults.[12]

In 1994 the WHO published a report entitled *Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis*,[13] while the National Osteoporosis Foundation of South Africa has published *'Guidelines for the early detection of osteoporosis and prediction of fracture risk'* (Table II).[14] In the WHO report the value of 2.5 SD below the mean of young healthy adult women at any site (spine, hip or radius) was chosen as the cut-off because this value identifies 30% of all postmenopausal women as having osteoporosis, which is approximately equivalent to the lifetime risk of fracture at any of these sites. This does not mean, however, that every woman with a BMD of 2.5 SD or less will necessarily have a fragility fracture in her lifetime, but only that this cut-off delineates a similar proportion of about 30% of the total population. Women with a BMD of more than 1 SD below but less than 2.5 SD below the young adult mean are categorised as having a 'low bone mass'. The occurrence of a fragility fracture greatly increases the risk of subsequent fractures over and above the risk associated with BMD alone. Women with a BMD of 2.5 SD below the mean who have had a fracture are categorised as having 'severe osteoporosis'. The publication of the WHO criteria was a major advance, but these diagnostic categories have some disadvantages in clinical practice. Patients who happen to fall below the arbitrary 'fracture threshold' of 2.5 SD below the mean are diagnosed as having osteoporosis, and such patients sometimes regard themselves as having acquired a serious or even life-threatening condition. Patients who are diagnosed as having 'low bone mass' may similarly take fright. In contrast, those above this arbitrary limit may regard themselves as not being at risk of fracture and not needing any preventive measures or treatment. A proposed classification according to degree of severity using the terms mild, moderate and severe (Table III) helps to overcome this problem and it should be explained to patients that bone density, fracture risk and the diagnosis of osteoporosis are a matter of degree.

Table II. Osteoporosis diagnostic categories[13]

Normal	BMD* or BMC* within 1 SD of ref. mean†
Low bone mass	BMD* or BMC* more than 1 SD below ref. mean† but less than 2.5 SD below this value
Osteoporosis	BMD or BMC* 2. 5 SD or more below ref. mean†
Severe osteoporosis	BMD* or BMC* more than 2.5 SD below mean† in the presence of one or more fragility fractures

*At any one site (spine, hip or radius).
†Mean and range of healthy young adult females.

NORMAL REFERENCE POPULATIONS

The values of BMD measured by different DEXA instruments vary depending upon the allowance made for bone fat and other factors. The 'normal' reference ranges also differ depending on the selection and size of the different 'normal' populations chosen by different investigators. Furthermore, the charts for 'normal' populations depend on the mathematical

Table III. Osteoporosis proposed diagnostic categories according to degree of severity

Normal	BMD of not more than 1 SD below ref. mean† at all sites measured
Low bone mass	BMD* of 1 SD or more but greater than 2 SD below ref. mean†
Mild osteoporosis	BMD* of 2 SD or more but greater than 3 SD below ref. mean†
Moderate osteoporosis	BMD* of 3 SD or more but greater than 4 SD below ref. mean†
Severe osteoporosis	BMD* of 4 SD or more below ref. mean† *or* BMD of 2 SD or more below mean† with one or more previous or existing fragility fractures

*At any one site at which BMD is measured.
†Mean and range of healthy young adult females.

methods used to calculate the means and ranges for the different age groups. The definitions of osteoporosis based on mean and SD of BMD were introduced to overcome the problem of differences in absolute measurements, but further investigations have revealed significant differences in the mean and SD measurements published by different manufacturers. Faulkner *et al.*[15] investigated the discrepancies in normative data between Lunar and Hologic DEXA systems. They measured the BMD of the lumbar spine and femur with both systems on the same day in 83 women aged 18 - 86 years, with an average age of 60 years. There were no clinically significant differences in the T-scores of the lumbar vertebrae, but on linear regression analysis there was a systematic difference of 0.9 SD in the T-scores of the femoral neck. Using the WHO definition of 2.5 SD below the mean of young adults, they found that 52% of women would be diagnosed as having osteoporosis of the femoral neck using the Hologic scanner but only 23% using the Lunar scanner. They then recalculated the means and SDs of the BMD of the femoral neck of young normal females for both the Hologic and Lunar systems using the NHANES III data,[16] and the revised values were then equivalent (Table IV). The prevalence of osteoporosis in the series with revised values was then approximately 30%, with both systems using WHO criteria. Simmons *et al.*[17] examined the problem in a group of 2 500 women aged 20 - 90 years and found that three out of four women were misdiagnosed as having osteoporosis using original Hologic QDR reference data. Faulkner *et al.*[15] proposed that normal means and ranges should be redefined for all densitometers using the NHANES III data to avoid discrepancies. They also suggested that the definition of osteoporosis should be revised from 2.5 SD to 2 SD below the mean of young normal subjects at the femoral neck, but stressed that these proposals should be confirmed through the establishment of consistent normative data. Manufacturers are now beginning to publish different 'normal' ranges and different criteria for the diagnosis of osteoporosis based on the NHANES III data. Proposed criteria for the diagnosis of osteoporosis according to degree of severity, as based on redefined absolute values of BMD derived from NHANES III database and the recommendations of Faulkner *et al.*, are given in Tables V and VI.

Table IV. Reported and redefined BMD values of lumbar spine and femoral neck[15]

BMD*	Hologic			Lunar		
(g/cm²)	Age	Mean	SD	Age	Mean	SD
L1 - L4 spine	30	1.047	0.11	20 - 45	1.180	0.12
Femur neck						
Reported	22	0.895	0.10	20 - 45	0.980	0.12
Redefined	20 - 29	0.85	0.11	20 - 29	1.00	0.11

*Healthy young adult females.

Table V. Osteoporosis diagnostic criteria of lumbar spine L1 - L4 based on redefined BMD values*[15]

Osteoporosis category	Definition (SD below mean)	Hologic (g/cm²)	Lunar (g/cm²)
Normal	≥ –1 SD	≥ 0.937	≥ 1.060
Low bone mass	–2 SD to –1 SD	0.827 - 0.936	0.940 - 1.059
Mild	–3 SD to –2 SD	0.717- 0.826	0.820 - 0.939
Moderate	–4 SD to –3 SD	0.607 - 0.716	0.700 - 0.819
Severe	< –4 SD	< 0.607	< 0.700

*Healthy young adult females.

Table VI. Osteoporosis diagnostic categories of femoral neck based on redefined BMD values*[15]

Osteoporosis category	Definition (SD below mean)	Hologic (g/cm²)	Lunar (g/cm²)
Normal	≥ –1 SD	≥ 0.740	≥ 0.890
Low bone mass	–2 SD to –1 SD	0.630 - 0.739	0.780 - 0.889
Mild	–3 SD to –2 SD	0.520 - 0.629	0.670 - 0.779
Moderate	–4 SD to –3 SD	0.410 - 0.519	0.560 - 0.669
Severe	< –4 SD	< 0.410	< 0.560

*Healthy young adult females.

INDICATIONS FOR BMD MEASUREMENT

The WHO Study Group and the National Osteoporosis Foundation of South Africa have published indications for bone densitometry. It is generally agreed that population screening is not justified on an epidemiological or cost-benefit basis. The use of BMD measurement is therefore restricted to the management of individual patients and the selective screening of high-risk groups. A simplified list of indications based on the guidelines of the National Osteoporosis Foundation are given in Table VII. There are other factors that need to be considered with regard to bone densitometry and the diagnosis of osteoporosis in clinical practice.

Table VII. Indications for bone densitometry

1. Past or present fragility fracture or any fracture in postmenopausal women
2. 'Osteopenia' or 'osteoporosis' suspected on radiograph
3. Medical/surgical disorders known to cause osteoporosis
4. Treatment with corticosteroids (> 5 g prednisolone daily or equivalent for > 6 months), cytotoxic or other drugs known to affect bone adversely
5. Assessment of peri- or postmenopausal women for possible HRT
6. Premature menopause and any amenorrhoea lasting longer than 6 months in women less than 45 years of age
7. Post-bilateral oophorectomy or post-hysterectomy in women 45 years of age or less with menopausal symptoms
8. Presence of one or more strong risk factors including family history of osteoporosis or fragility fracture
9. Monitoring response to treatment of osteoporosis

1. The predictive value of clinical risk factors to identify individual patients with osteoporosis is low. More than half of the individuals without risk factors will develop osteoporosis and many with risk factors will have normal BMD.

2. Measurements of BMD are only justified when they affect patient management. If women are already on hormone replacement therapy (HRT) and are not concerned about osteoporosis or the risk of fracture then measurement of BMD serves little purpose.

3. Assuming that facilities are available and that cost is no consideration, then individuals are entitled to request BMD measurement in order that they may be informed about their BMD and future risk of fracture. This may help to allay unwarranted fears and enable individuals to decide whether or not to embark on therapy.

4. Repeat BMD measurements are essential in order to monitor response to treatment. In a personally observed series of 100 postmenopausal women on HRT who had repeat DEXA measurements approximately annually, 60% showed a significant increase in BMD, 30% were within the range of measurement error and were regarded as unchanged, but 10% of women showed a significant fall in BMD of either the femur or spine in spite of therapy. Such patients require investigation and additional treatment to prevent further bone loss. It is therefore recommended that all patients being treated for osteoporosis should ideally have BMD measurements annually, at least initially. The intervals between measurements can be extended gradually in patients who have a progressive increase in BMD or whose BMD measurements are in the 'low bone mass' range. Most patients are keen to know how they are progressing and repeat measurements are often of considerable value in ensuring continuation of therapy.

5. The absence of facilities for bone densitometry is no bar to the prophylaxis or treatment of osteoporosis, even though the diagnosis may be presumptive and less certain. Ideally all women should commence HRT at the menopause to prevent bone loss and osteoporosis. Bone density may be increased by appropriate therapy. It may, however, not be possible to restore normal bone architecture completely in patients who have already developed osteoporosis.

WHEN TO MEASURE BMD

The age at which BMD should be measured in the absence of any special risk factors such as premature menopause depends upon the clinical situation and the purpose of the measurement. The peak bone mass at the menopause is the best guide to the future development of osteoporosis although the prevalence of osteoporosis at this time is low. If the aim is to provide an estimate of future risk with a view to starting preventive therapy, then BMD is best measured at the menopause. Treatment can then be started immediately and bone loss and osteoporosis may be prevented. However if the aim is to diagnose osteoporosis, BMD is best measured between 60 and 65 years of age. By this time women will have passed through the acute phase of postmenopausal bone loss but there is still sufficient time to initiate therapy and to prevent vertebral and, more importantly, hip fractures that occur when women are in their 70s and 80s. It is probably never too late to measure BMD or to start treatment. Even if treatment for osteoporosis is only started at age 70 the incidence of hip fracture is still significantly reduced.[18] In practice the timing of BMD measurement is often determined by the age at which the patient first presents and her wishes regarding treatment.

References

1. Dalen N, Hellstrom L, Jacobson B. Bone mineral content and mechanical strength of the femoral neck. *Acta Orthop Scand* 1976; **47:** 503-508.
2. Nguyen T, Sambrook P, Kelly P, *et al.* Prediction of osteoporotic fractures by postural instability and bone density. *BMJ* 1993; **307:** 1111-1115.
3. Faulkner KG, Cummings SR, Black D, *et al.* Simple measurements of femoral geometry predicts hip fracture: The study of osteoporotic fractures. *J Bone Miner Res* 1993; **8:** 1211-1217.
4. Kanis J. *Osteoporosis.* Oxford: Blackwell Science, 1994: 49.
5. Melton LJ. Differing patterns of osteoporosis across the world. In: Chestnut CH III, ed. *New Dimensions in Osteoporosis in the 1990's.* Hong Kong: Excerpta Medica Asia, 1991: 13-18.
6. Salamone LM, Ferrell R, Black DM, *et al.* The association between vitamin D receptor gene polymorphisms and bone mineral density at the spine, hip and whole body in premenopausal women. *Osteoporos Int* 1996; **6:** 63-68.
7. Cummings SR, Black DM, Nevitt MC, *et al.* Bone density at various sites for prediction of hip fractures. *Lancet* 1993; **341:** 72-75.
8. Ito M, Tsurusaki K, Hayashi K. Peripheral QCT for the diagnosis. *Osteoporos Int* 1997; **7:** suppl 3, S120-S127.
9. Morita R, Yamato I, Yuu Y, *et al.* Quantitative ultrasound for the assessment of bone status. *Osteoporos Int* 1997; **7:** suppl 3, LS128-LS134.
10. Hans D, Dargent-Molina P, Schott AM, *et al.* Ultrasonic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet* 1996; **348:** 511-514.
11. Kanis J. *Osteoporosis.* Oxford: Blackwell Science, 1994: 7.
12. Newton-John HF, Morgan DB. The loss of bone with age, osteoporosis and fractures. *Clin Orthop* 1970 **71:** 229-252.
13. World Health Organisation. *Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis.* Geneva: WHO Technical Report Series 843, 1994.
14. Council of the National Osteoporosis Foundation. Guidelines for the early detection of osteoporosis and prediction of fracture risk. *S Afr Med J* 1996; **86:** 1113-1116.
15. Faulkner KG, Roberts LA, McClung MR. Discrepancies in normative data between Lunar and Hologic DXA systems. *Osteoporos Int* 1996; **6:** 432-436.
16. Looker AC, Wahner HW, Dunn WL, *et al.* Proximal femur bone mineral levels of US adults. *Osteoporos Int* 1995; **5:** 389-409.
17. Simmons A, Simpson DE, O'Doherty MJ, Barrington S, Coakley AJ. The effects of standardization and reference values on patient classification for spine and femur dual-energy X-ray absorptiometry. *Osteoporos Int* 1997; **7:** 200-206.
18. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. *Ann Intern Med* 1995; **122:** 9-16.

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