Controversies in the Management of Osteoporosis

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"This is to acknowledge that Craig Rubin, M.D. has a consultant relationship with Proctor & Gamble."

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There have been considerable recent advances made in the understanding and treatment of osteoporosis. As our knowledge expands, not surprisingly, there are also areas of controversy and uncertainty in the assessment and management of patients. In this grand rounds, I will review some of the more frequently confronted issues in the management of postmenopausal osteoporosis.

Evolving Definitions

The definition and clinical diagnosis of osteoporosis has evolved over the past 15 years. Prior to 1990 osteoporosis was characterized as a reduction in mass of bone per unit volume to a level below that required for adequate mechanical support function. In 1990 and 93, consensus development conference panels defined osteoporosis as "a disease characterized by low bone mass, microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" (1,2). This definition recognized the importance of bone microarchitecture and its importance to bone strength. In 1994, an expert panel of the World Health Organization (WHO) published an operational definition of osteoporosis based on a bone mineral density of 2.5 standard deviations or less below the mean for young white adult women (or a T-score of -2.5)(3). In 2000, an NIH Consensus Conference on osteoporosis modified the definition and defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture (4). The two main determinants of bone strength are bone density and bone quality. Bone density is expressed as grams of mineral per area or volume. Bone quality refers to architecture (5), turnover (6), damage accumulation (7) (e.g., microfractures) and mineralization (8). A fracture occurs "when a failure-inducing force (e.g., trauma) is applied to osteoporotic bone. Thus, osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made". See Table 1.

Table 1

Risk Factors Affecting Bone Metabolism
Prolonged amenorrhea
Diet low in calcium
Minimal sun exposure
Smoking
Excessive alcohol intake
Inactivity or prolonged immobilization
Low body weight
Medication Use: (≥ 7.5 mg/d of prednisone for > 6 mo), phenytoin, excessive thyroid replacement, GRH agonist/antagonist
Secondary Osteoporosis: (primary HPTH, primary hypogonadism, multiple myeloma, malabsorption, thyrotoxicosis, others)

Risk Factors for Fracture
≥ 80 years old
Long-acting benzodiazepine therapy
Low weight (<58 kg)
No walking for exercise
Inability to rise from chair/lower extremity dysfunction
Poor depth perception
Poor distant vision
Neurologic conditions: stroke, Parkinson's, dementia.

The consensus statement goes on to say that "currently there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70 percent of bone strength (4). The WHO definition, which has gained wide acceptance, uses bone density in young white women as a standard (3); it is not clear how to apply this diagnostic criterion to men, children, and across ethnic groups. In addition, the consensus points out the difficulty in accurate measurement and standardization between instruments and sites and the resulting controversy that exists among experts regarding the continued use of this diagnostic criterion.(4)" Although bone density remains an important predictor for fractures, it should be emphasized that bone density is a risk and the outcome or event of consequence is a fracture. The WHO criteria were generated around the risk of a population for fracture and not individual patients. Some contest that the WHO criteria has been misapplied to individual patients. Although BMD can predict fractures, there is a wide overlap among those who fracture and those who do not (9).

The WHO Criteria for Osteoporosis and BMD as a Surrogate of Bone Strength

The primary reason for use of BMD as defining osteoporosis is that BMD is the single most powerful predictor of fracture risk. It is as predictive for future fractures as other common screening tools used to predict cardiovascular events such as cholesterol and blood pressure measurements (10). White women whose bone mass is more than 2.5 SD below the mean normal peak bone mass are termed osteoporotic because over 95% of those who ultimately fracture have bone mass values below this level (3,11). However, the risk is continuously distributed and the lower the BMD the greater the risk, independent of age. Again, this is not unlike blood pressure and cholesterol levels. Therefore, it is legitimate to compare any individual's bone density to the density of a young individual's peak mass. Also, the diagnosis is not defined on the basis of age-matched data since it would imply that the prevalence of osteoporosis does not increase with age as it does. The WHO criterion also identifies patients with smaller reductions in BMD (12) as osteopenic (T-scores from -1 to -2.5). However, the "cut-off" level of –1.0 was arbitrarily chosen. It is used to identify women whose bone density was below normal for young adults. The term has been criticized because it includes a broad range of women, some with varying risks of fracture and some suggest it is more useful and less alarming to avoid this term and focus on fracture risk instead. Nonetheless, if patients are aware that their BMD is low, they and their physicians can make decisions how to monitor or prevent further loss. The evidence that treating women with BMD in this range prevents fractures is not clear.

Although risk factors for low BMD can be elicited from the medical history, such information only identifies about 60% of those with a low bone density (14).

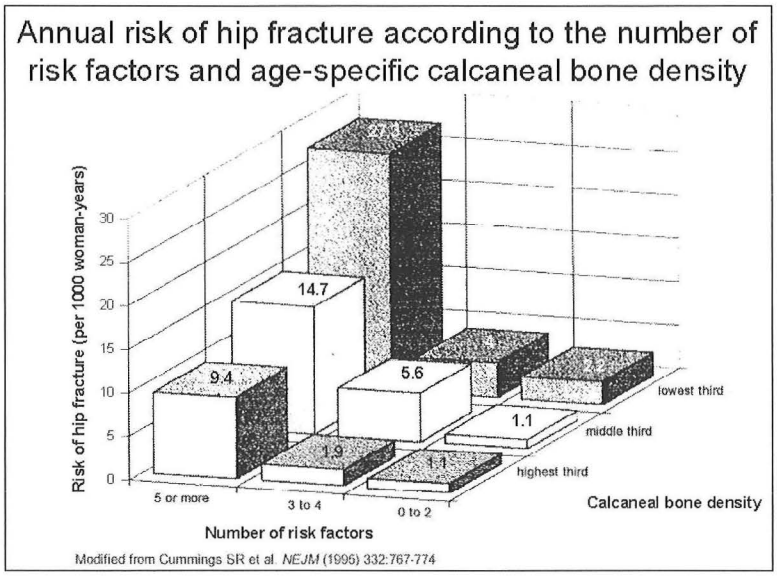
Beyond BMD and Fracture Risk

In addition to bone density there are other factors that are independently related to fracture risk. These factors include pre-existing fragility fractures (15-17), age (10), maternal history of hip fracture (18), sedentary lifestyle (18), small body size (<58 kg)(19), fall risks (e.g., poor vision, dementia, certain medications, Parkinsonism), and reduced functional status (20). A prevalent vertebral fracture increases the risk of a second fracture at least two-fold (usually 4-5)

independent of bone mass (21). The combination of low bone mass and one vertebral fracture may increase the relative risk of second fractures as much as 25-fold (22). Therefore, the risk assessment in any single patient should take into consideration individual patient factors in addition to bone density to assess the fracture risk (18). In the MORE trial (23), the number needed to treat (NNT) to prevent to a new vertebral fracture was reduced from 113 to 42 in women with a prevalent fracture at baseline compared to those without. However, patients with prevalent fractures often do not get screened. In one study, patients with vertebral fractures incidentally found on a chest x-ray were rarely screened for osteoporosis or received appropriate therapy (24).

Cummings, et al. (18) described the relationship between risk factors for hip fracture and BMD in older community dwelling white women. The cumulative effect of multiple risk factors and low BMD posed the greatest risk. The rate of hip fractures in women in the lowest BMD tertile with 0-2 risk factors increased nearly 14 times if the number of risk factors increased to 5 or more for the same tertile of BMD. Women in the highest BMD tertile but with five or more risk factors were nine times more likely to have a hip fracture than the lowest BMD tertile and 0-2 risks. In comparison the annual risk of hip fracture only doubled going from the lowest BMD tertile to the highest.

Figure 1



Variable BMD Response to Therapy but Similar Reductions in Fracture Risk

Although the comparison of BMD and fracture risk and cardiovascular risk factors and their outcomes are commonly made, the response to treatment is very different. In the case of hypertension, the elevated blood pressure measurement can ordinarily be returned to normal. Similarly, reducing cholesterol levels to normal levels can often be achieved with associated risk reduction. The same cannot be said for osteoporosis. Typically, even after pharmacologic treatment, BMD values remain in the osteoporotic range in many patients.

It is predicted that for each SD below peak BMD there is an associated two-fold increased risk for vertebral fractures (25). In an earlier study by Liberman, et al. (26) in which alendronate showed an approximately 50% relative risk reduction in vertebral fractures, BMD had increased nearly a standard deviation (1 SD is approximately equal to a 10% gain in BMD) and the apparent relationship between T-score doubling (or reducing in this case) and risk reduction appeared to hold. From the authors discussion,

> "In addition, the overall increase in spine bone mineral density in the alendronate group (approx 8.8 percent, as compared with a decrease in the placebo group) was associated with an almost 50 percent decrease in the proportion of women with new vertebral fractures. These findings confirm the results of other studies indicating that the relative risk of a vertebral fracture approximately doubles for each reduction in spine bone mineral density equivalent to 1 SE (approximately 10 percent)."

However, subsequent clinical trials have shown smaller increases in bone density increments with similar reductions in fracture rate (27). See Table 2.

Summary of Different Vertebral Fracture Studies

Study	*Increase in spine BMD*	*Reduction in vertebral FX*	*Spine T-score*	*Baseline vertebral Fx*
FIT II	8.3%	44%	-2.1	0%
FIT I	7.9%	47%	-2.5	100%
RVE	7.1%	49%	-2.8	100%
RVN	5.4%	41%	-2.4	100%
MORE	2.6%	40%	-2.6	37%
PROOF	1.2%	36%	<-2.0	100%

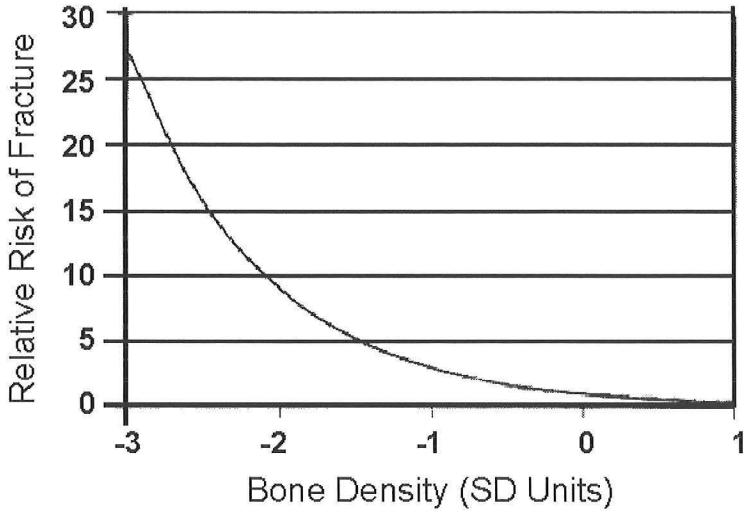
Faulkner KG. *J Bone Min Research* 15:183-187, 2000

Table 2

The explanation for the variance and discordance in effect size and outcomes is of great interest and underscores how much we still need to learn to fully understand fracture risk and bone strength. Faulkner proposed three explanations for the observed differences in BMD response and fracture reduction with different therapeutic agents: 1) Non-density-related effects of therapeutics, (fracture risk is also related to factors other than BMD -- age, propensity to fall, skeletal geometry, bone turnover, and others -- all contribute to the outcome of fracture)(27). 2) Technical limitations of measuring BMD changes and differences in skeletal fragility of the study population and 3) hysteresis effects in the BMD/fracture risk relationship.

The size of the fracture risk reduction may vary depending on the baseline BMD of the study population and the location on the curve describing the relative risk/BMD relationship (see Fig. 2). This suggests that smaller changes in BMD could be sufficient to reduce fractures in those with lower baseline BMD.

Figure 2



There is some evidence that reducing bone resorption and markers of bone remodeling is the most important aspect to reducing fracture risk (29). Reduction in resorption has influences at the microarchitectural level, which affects fracture risk and bone strength. However, markers of bone turnover are currently not reliable enough to be used for diagnosis or routine management of osteoporosis (30).

Variability in Classifying Patients at Different Sites and Devices

The WHO criteria for the assessment of osteoporosis are based on a BMD at any skeletal site (although originally related peripheral measurements to hip fracture). However, variation can be found in diagnosing osteoporosis using the WHO criteria depending on the site measured. Greenspan, et al. (31) studied 129 elderly women and showed that the prevalence of osteoporosis varied depending at which skeletal site was measured. At the PA spine < 30% of patients had a –2.5 T-score compared to 65% for measurements taken at the lateral spine. Discrepancies were also noted for measurements at the proximal femur.

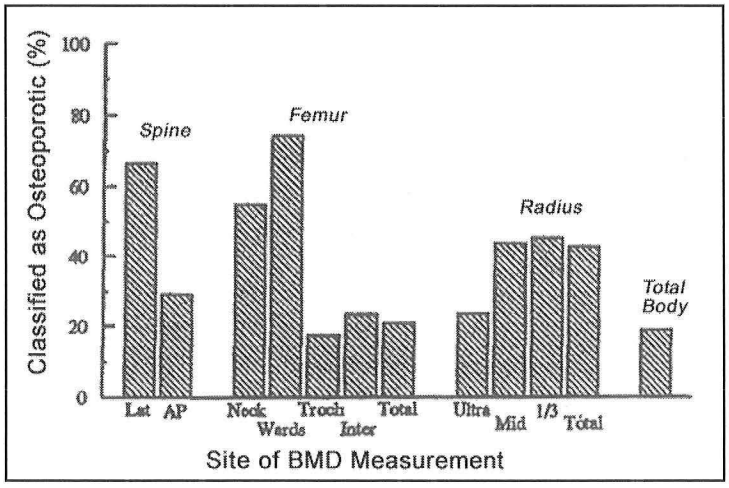
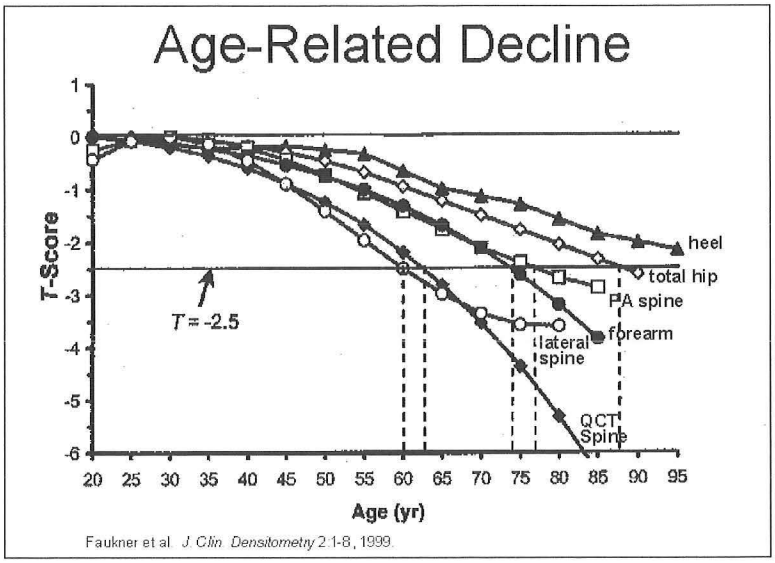


Figure 3

Faulkner (27) showed the age-related decline in mean Caucasian female T-scores for BMD technologies based on manufacturers reference ranges.

Figure 4



The T-score at the spine showed the largest age-related decline whereas hip and heel T-scores declined less so. The prevalence estimates using the WHO criteria for osteoporosis at age 60 years ranged from 50% at the spine to a low of 3% at the heel. Using the National Osteoporosis Foundation (NOF) therapeutic threshold of -1.5 (NOF recommends interventions if -1.5 or less if accompanied by any risk factors) for postmenopausal women, therapy would be recommended for 84% of 60-yr-old women based on spinal QCT measures compared to 20 and 29% based on heel and hip measures (32). The International Society of Clinical Densitometry caution against applying WHO T-scores to modalities other than DEXA. The discrepancies in observed T-scores among different skeletal sites and devices could be due to: 1) discordance in age-related BMD losses at different sites (31); 2) differences in the reference ranges among different machines (33,34); and 3) technical differences between techniques themselves.

This variability of T-score findings raise the issue that a single T-score criterion cannot be universally applied to all BMD measurements. The site with the strongest relationship to hip fracture risk (hip and heel) showed the least age-related T-score decline and lowest estimate prevalence. Although all sites have utility in predicting hip fracture risk they are less sensitive than the hip itself (35).

Abrahamsen, et al. (36) reported that among the one-half of women who had significant decreases in spine BMD within five years of menopause showed no significant fall in forearm BMD. The hip and spine were the most reliable sites to monitor skeletal site response to treatment or to assess bone loss in untreated women.

Racial Differences in BMD

Asian women have much lower bone densities than Caucasian women, yet hip fracture incidence is lower than in white women. This finding has cast doubts about the predictive ability of BMD and hip fracture (37). However, these disparities may be related to other factors. Currently normative data used by bone density machines are frequently not matched for non-female, non-white populations raising the concern of the applicability of bone density measurements. Furthermore, some studies have found that BMD does not differ in Asian women and men compared to Caucasians after controlling for weight, height and other factors (38,39). Others have found that skeletal size accounts for racial differences (40). When evaluating non-Caucasian women, it is important to know what racial group composes the reference population. Prospective studies relating BMD and fracture in white women allow measures of BMD to be translated into risks of fracture in this particular population. However, similar studies have not been done for men or non-white women.

BMD Site Selection

Although there is discordance between bone sites, a low measurement at one site is predictive for fracture at other sites. However, if one is concerned about hip fractures, the hip is the best site to measure. Furthermore, some recommend hip measurements for those at least 70 years old because the presence of osteophytes, facet sclerosis, and other degenerative and aortic calcifications can result in falsely elevated measurements. Lastly, most randomized controlled trials, which serve as the basis for clinical practice, have commonly used lumbar and/or hip measurements (in particular femoral neck and total). In most cases it is desirable to assess both central measurements (hip and spine); there is little indication for the need to measure peripheral sites. There is enough discordance that a normal measurement at a peripheral site, such as the finger, is insufficient to exclude osteoporosis. A low BMD at a peripheral site should be further evaluated by a central measurement to assess risk more precisely. In early postmenopausal women the spine may have an advantage over the hip and in late postmenopausal woman the hip has advantages over the spine. Again, discordance is sufficiently high (15% or more) that for an individual patient over 65 years of age it appears reasonable to obtain both hip and spinal measurements.

Serial Measurements of Bone Mineral Density

The proper interpretation of serial bone density measurements is important. Misinterpreting BMD changes can lead to an erroneous assessment and decisions regarding management. Clinicians need to be aware of the concept of clinically least significant change (CLS) when interpreting BMD results. The BMD interpretation report should note whether the changes between serial measurements are of significance. In order to determine the CLS change, the precision error (percent coefficient of variation) of the measurements needs to be known. The precision error is the amount of random variation (noise) observed by repeat testing in a patient not caused by a biological change. The precision error is typically 1% for DXA equipment at the lumbar spine BMD and 1.5% for the femoral neck BMD in normal young subjects (42-46). The precision error is larger in postmenopausal women than younger woman (43). The precision

error of the technique multiplied by 2.8 determines the clinically least significant (CLS) or size of change needed to be considered a "real" change in values (41). The 2.8 multiplier determines the smallest change required to have 95% confidence of a 'real' change. The 2.8 comes from the product of: 1.96 (for 95% confidence level) times the square root of 2. The CLS is really the least statistically significant change. Therefore, a 2 percent decline in lumbar or femoral neck BMD is not a statistically significant change in BMD and may or may not indicate a real change in BMD nor signal a failure to respond to medications. (For research studies, 95% confidence (or 2.8* precision) is often used. In clinical practice, less stringent levels, 80% or 90% can be used. The multipliers in this case would be 1.8 or 2.3, respectively). Bone densitometry, with co-efficient variations of 1 to 2 percent is one of the most precise measurements in clinical medicine. The USPSTF suggested that screening BMD more often than every 2 years is unwarranted because the size the precision error of densitometry exceeds estimated bone loss in less then a 2-year period (47). On the other hand if treatment is expected to increase BMD in excess of 3% in the first year of therapy, a repeat BMD at 12 months would be reasonable. Of note, other measurements such as cholesterol, blood pressure and spirometry have larger coefficients of variation then BMD measurements (48).

Regression to the Mean

Another complexity in the interpretation of BMD values is the principle of regression to the mean. Cummings, et al. (49) analyzed the bone density changes in patients participating in the FIT (alendronate)(50) and MORE (raloxifene)(23) trials. In the FIT study (50), 18% of subjects had no change or a decrease in total hip BMD in the first year. Those who lost the first year tended to gain the second year. On average, those who lost the most during the first year were the most likely to gain hip BMD and gain more than other groups during the second year of treatment. For example, those who appeared to lose more than 4% during the first year had a 92% chance of gaining BMD and, on average, gained 4.8% during the next year of continued treatment. In contrast, those who seemed to have gained more than 8% the first year, had only a 36% chance of gaining BMD in the second year and, on average, lost 1% during the second year of treatment with alendronate. A similar phenomenon was seen in women in the placebo group. In that group, the 37 who lost more than 4% of their hip BMD in the first year had an average increase in the second year of 4.8%. While among the 61 who gained more than 8% experienced an average loss of 1% during the second year. In the MORE trial, women who lost BMD in the femoral neck during the first year of taking Raloxifene usually gained BMD during the second year of treatment. Women who appeared to lose more than 4% during the first year had a 79% chance of gaining BMD and, on average, gained 4% during the next year of continued treatment and those who gained 8% the first year had only a 22% chance of gaining BMD the second year, and on average lost 2.8% during the second year of treatment with Raloxifene. The authors' stress that regression to the mean is the natural correction of random error in the measurement of bone density and the increases and decreases the first year of therapy should not be interpreted as resistance to therapy. Of course, patients with bone loss on treatment need to be monitored and questioned regarding medication adherence and proper administration. These findings bring into question whether BMD should be used to monitor patients treated with antiresorptive agents. Those who did have a decline in BMD may have had a larger decline without treatment. Arguments in favor of monitoring response to therapy is that patients demand this feedback and

that over time BMD is still a useful guide to evaluate response to therapy, although informed interpretation of results is essential. These findings suggest that physicians should not stop or change therapies with demonstrated efficacy solely because of modest loss of bone density.

Is the Impact of Osteoporosis Exaggerated?

The estimated cumulative lifetime fracture rates are reported as high as 50% for white postmenopausal women (51). However, this figure includes all fractures. Overwhelmingly, the morbidity and mortality associated with osteoporosis is related to hip fractures, to a lesser extent vertebral fractures and a much lesser extent other fractures. The impact of a Colles fracture and a hip fracture (although both occur after a fall) have very different consequences. So more precisely, a 65-year-old white woman who lives to age 90 has an estimated 14-16% chance of sustaining a hip fracture and (4,52,53) a 28% and 10% chance of sustaining a vertebral or Colles fractures, respectively.

There are currently an estimated 300,000 hip fractures annually (54). Nearly one-third of patients with hip fractures are discharged or placed in nursing homes within the year following a fracture. The 1-year mortality after sustaining an osteoporotic hip fracture is approximately 20 percent (87). Hip and vertebral fractures are a particular problem for women in their late 70s and 80s (4). Eighty percent of women older than 75 years preferred death to a bad hip fracture resulting in nursing home placement. Regardless of the percent of patients with osteoporosis, the prevalence of osteoporotic fractures will continue to increase (55) since the proportion of the population over 65 years and older is increasing dramatically.

Hip fractures are the result of factors related to a fall and bone strength. A fall results in conversion of potential energy to kinetic energy. The force of the fall (kinetic energy) must be directed away from the hip and/or the net resultant force must be absorbed and dissipated sufficiently to avoid fracture, that is, the strength of the bone based on bone mineral content and bone quality. A person landing close to his/her hip is more likely to fracture (56). Age-related changes in the compensatory response to a falls and direction of falls and other risk factors make the elderly more vulnerable to hip fractures then younger patients (18,57). Greenspan, et al. found that in women who sustained hip fractures after a fall, bone density was a significant associated risk; but there is significant overlap in BMD among those who fractured and those who did not. The direction of fall had the highest association with those who fell and fractured. With aging there are a number of factors that increase the risk to fall and result in forces aimed directly at the hip. Since it is unlikely that pharmacologic interventions can increase bone strength more than normal bone, it is likely that such interventions will have only a modest effect at preventing hip fractures. Furthermore, if people did not fall, the annual incidence of hip fractures would most likely be closer to 30,000 versus 300,000 a year. (It is estimated that at least 90% of hip fractures are the result of falls (58). Clearly, the most important therapeutic intervention to prevent hip fractures would be to prevent falls. However, our current ability to prevent falls is limited. What is the evidence, and to what degree, do pharmacologic agents prevent hip fractures?

What Evidence Exists to Support Pharmacologic Interventions in the Prevention of Hip Fractures?

A number of large randomized trials have been published reporting fracture outcomes (23,26,28,50,59-62). Most have focused on vertebral fractures as the primary outcome and have included patients with or without baseline fractures and therefore with varying degrees of disease severity. All have reported hip fracture outcomes, which will be reviewed here. These studies have included the use of estrogen, alendronate and risedronate, and calcitonin (see Table 3). To date, only one randomized controlled trial has been conducted with hip fracture as the primary outcome. In addition, the Women's Health Initiative (WHI) is a randomized controlled primary prevention trial in which hip fracture was a secondary outcome (63).

Table 3

Women with ≥ 1 Incident Hip Fracture			
Therapeutic Agent	Placebo (*)	Treatment (*)	RR (95% CI)
Raloxifene [n=7705, av. age=67] Ettinger B et al. *JAMA* 1999; 282(7):637-645.	0.7% (18)	0.8% (40)	1.1 (0.6-1.9) NS
Alendronate [n=994, av. age=64] Liberman UA et al. *N Eng J Med* 1995, 333:1437-1443.	0.8% (3)	0.2% (1)	NS
Alendronate [n=2027, av. age=71] Black DM et al. *Lancet* 1996, 348(9041):1535-1541.	2.2% (22)	1.1% (11)	0.49 (0.23-0.99)
Alendronate [n=4432, av. age=68] Cummings SR et al. *JAMA* 1998; 280:2077-2081.	1.1% (24)	0.9% (19)	0.79 (0.43-1.44) NS
Risedronate (all VFX) [n=2458, av. age=68] Harris ST et al. *JAMA* 1999; 282(14):1344-1352.	1.8% (15)	1.5% (12)	NS
Risedronate [n=1226, av. age=71] Reginster JY et al. *Osteop Int* 2000; 11:83-91.	2.7% (11)	2.2% (9)	NS
Risedronate [n=9331, av. age=74 and 83] McClung MR et al. *N Eng J Med* 2001, 244(5):333-340.	3.9% (95)	2.8% (137)	0.7 (0.6-0.9)

* = number of hip fractures. RR = Relative Risk
Modified from Marcus R et al. *Endocr Rev* 2002; 23(1):16-37.

Estrogen is an effective antiresorptive agent. It has long been used to prevent bone loss and treat osteoporosis but there have been very few well-designed randomized studies to evaluate its efficacy (64). When compared to alendronate in a randomized controlled trial of osteopenic women, mean age 62 years, there was no difference between groups in the gain in vertebral BMD at 24 months and biochemical markers of bone turnover were similarly reduced (65).

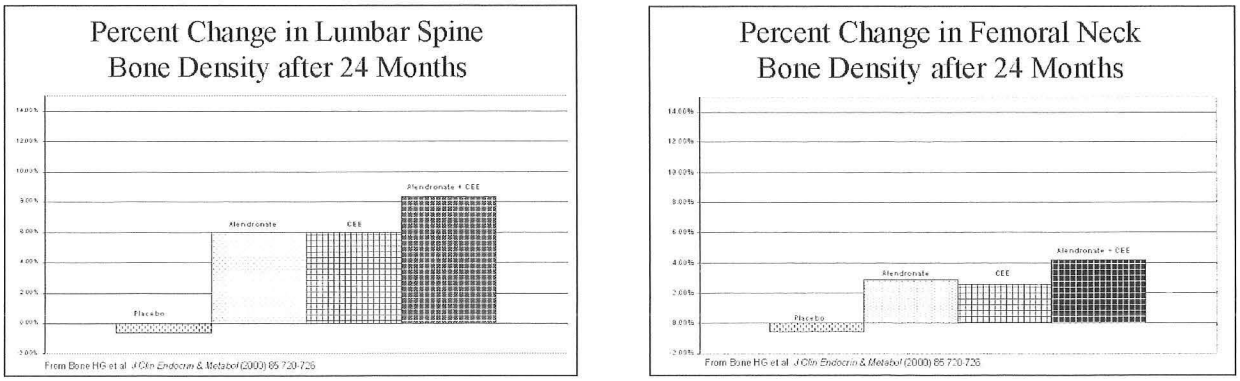


Figure 5

The use of estrogen in prevention of hip fractures has long been reported. However, this evidence comes from observational studies. The evidence supporting estrogen's efficacy in preventing hip fractures is in women on therapy between 50 and 70 years of age. There is less evidence after this age (66-71).

The recently reported WHI trial found that postmenopausal women taking conjugated equine estrogen and medroxyprogesterone (hormonal replacement therapy-HRT) were less likely to suffer a hip or other osteoporotic fracture (63). The conjugated equine estrogen alone arm of the study is ongoing. Of note, this was a primary prevention trial in relatively healthy postmenopausal women. (Therefore, the risk of fracture in enrolled subjects was lower than in a group of known osteoporotic patients, making it harder to show efficacy). The study group involved relatively young women (mean age 63). The incidence of hip fractures increases substantially after the age of 75. Nonetheless, subjects enrolled in the conjugated equine estrogen group had fewer hip fractures as well as other fractures (see Tables 4 and 5). The NNT to prevent one hip fracture was 403. The NNT to prevent one vertebral or any osteoporotic fracture was 387 and 48, respectively. The NNT to cause harm can also be calculated. The NNT to cause one additional case of invasive breast cancer was 237. The NNT to treat to cause an additional case of deep venous thrombosis was 141 and pulmonary embolus was 227. The mean duration of treatment was 5.2 years.

Table 4

Clinical Outcome	# Events		Probability		ARR	1/ARR	NNT	NNT
	Est+Prog	Placebo	Est+Prog	Placebo	Plac-Rx	NNT	Benefit	Harm
Fractures			0.0000	0.0000				
Hip	44	62	0.0052	0.0077	0.0025	403.29	**403**	
Vertebral	41	60	0.0048	0.0074	0.0026	386.78	**387**	
Other osteoporotic	579	701	0.0681	0.0865	0.0185	54.19	**54**	
Total	650	788	0.0764	0.0973	0.0208	47.98	**48**	
Cancer								
Invasive breast	166	124	0.0195	0.0153	-0.0042	-237.49		**237**
Endometrial	22	25	0.0026	0.0031	0.0005	2003.01	**2003**	
Colorectal	45	67	0.0053	0.0083	0.0030	335.66	**336**	
Total	502	458	0.0590	0.0565	-0.0025	-401.94		**402**
Death			0.0000	0.0000				
Due to other causes	165	166	0.0194	0.0205	0.0011	916.85	**917**	
Total	231	217	0.0272	0.0268	-0.0004	-2675.30		**2675**
Global index	751	623	0.0883	0.0769	-0.0114	-87.75		**88**

NNT = number of patients needed to be treated for one additional patient to benefit or be harmed
ARR = Absolute Risk Reduction
J Am Med Assoc 2002; 288:321-333.

Table 5

Clinical Outcome	# Events		Probability		ARR	1/ARR	NNT	NNT
	Est+Prog	Placebo	Est+Prog	Placebo	Plac-Rx	NNT	Benefit	Harm
Cardiovascular								
CHD	164	122	0.0193	0.0151	-0.0042	-236.83		**237**
CHD death	33	26	0.0039	0.0032	-0.0007	-1491.36		**1491**
Nonfatal MI	133	96	0.0156	0.0118	-0.0038	-264.05		**264**
CABG/PTCA	183	171	0.0215	0.0211	-0.0004	-2449.03		**2449**
Stroke	127	85	0.0149	0.0105	-0.0044	-225.26		**225**
Fatal	16	13	0.0019	0.0016	-0.0003	-3616.86		**3617**
Nonfatal	94	59	0.0111	0.0073	-0.0038	-265.33		**265**
Venous thromboembolic disease	151	67	0.0178	0.0083	-0.0095	-105.46		**105**
Deep vein	115	52	0.0135	0.0064	-0.0071	-140.81		**141**
Pulmonary embolism	70	31	0.0082	0.0038	-0.0044	-227.10		**227**
Total Cardiovascular disease	694	546	0.0816	0.0674	-0.0142	-70.43		**70**

NNT = number of patients needed to be treated for one additional patient to benefit or be harmed
ARR = Absolute Risk Reduction

J Am Med Assoc 2002; 288:321-333.

The HRT arm of the WHI trial confirms the favorable effect of HRT on bone and in preventing hip fractures. The benefit, however, is modest and a number of significant adverse effects were also more likely in this group. Furthermore, as in most published studies to date, subjects were less than 70 years old. Because the incidence of hip fractures increases significantly after age 75, we have little data from those most likely to sustain hip fractures. The risks associated with estrogen treatment from the WHI trial are often noted to be small but the benefits may be even smaller for the age group studied.

In a randomized controlled trial, McClung, et al. evaluated the effect of risedronate on the incidence of hip fractures among elderly women as their primary outcome (see Table 6). The study enrolled 9331 subjects. This included 5445 women age 70 to 79 with osteoporosis and another group of 3886 women at least 80 years of age enrolled on the basis of at least one nonskeletal risk factor for hip fractures or an osteoporotic femoral neck BMD (about 20% of this group). Overall treatment with risedronate provided a 1.1% absolute risk reduction. The most benefit was seen in women between 70-79 years of age who experienced a 1.3% (RR 40%) absolute risk reduction. For those with a prevalent vertebral fracture at baseline, the absolute risk reduction was higher at 3.4%. For those over 80 years of age selected only for risk factors, there was no significant reduction in hip fracture.

These findings have often been interpreted as showing evidence that those over 80 years may sustain hip fractures for reasons other than osteoporosis. But this may not be an accurate assessment of the results. Firstly, about 80 percent of subjects in the over 80 group did not have BMD measured and therefore constitutes speculation about the 80 percent without BMD values that may be unfounded. Secondly, age by itself is a risk for declining bone strength independent of BMD. Thirdly, those over 80 years (as documented to a limited degree in this group) are likely to have risks for fractures and falls (see Table 1). These factors overlap and are likely to

exceed the modest increase in bone strength that pharmacologic agents provide in this high risk age group.

Table 6

Group	Risedronate			Placebo			Relative Risk (95% CI)	P Value*	ARR
	Total #	# hip fracture	Incidence	Total #	# hip fracture	Incidence			
			%			%			
Overall	6197	137	2.8	3134	95	3.9	0.7 (0.6-0.9)	0.020	1.1
Women 70-79 yr of age with osteoporosis	3624	55	1.9	1821	46	3.2	3.2 (0.4-0.9)	0.009	1.3
Presence of vertebral fracture at base line	1128	22	2.3	575	0.25	5.7	0.4 (0.2-0.8)	0.003	3.4
Absence of vertebral fracture at base line	1773	14	1	875	12	1.6	0.6 (0.3-1.2)	0.140	0.6
Women ≥80 yr of age with ≥1 clinical risk factor for hip fracture	2573	82	4.2	1313	49	5.1	0.8 (0.6-1.2)	0.350	0.9

* P values for the comparison between risedronate and placebo by the log-rank test (two-sided).
** The presence or absence of a vertebral fracture at base line was known for 4351 (80%) of the women 70-79 years old.
McClung MR et al. *NEJM* 2001; 344(5):333-340.

A number of clinical trials have been completed assessing the use of alendronate on fracture outcomes. The FIT evaluated the effects of alendronate on bone mass and fractures in osteoporotic women (femoral neck BMD T score <-1.6) between 54 and 81 years of age with and without fractures. In the group, without prevalent fractures Cummings, et al. (50), followed 4,432 women, mean age 68 years, for an average of 4.2 years and found no overall reduction in hip fractures. However, in a post-hoc analysis of those with a femoral neck BMD less than –2.5 there was a statistically significant 1.2% absolute risk reduction (NNT 81) in hip fractures. In those with a femoral neck T-score above –2.5, there was no reduction in hip fractures (0.4%) in the placebo and 11 (0.8%) in the alendronate group (CI, 0.70-5.36). In the FIT study of women with a prevalent fracture, Black, et al. (59) followed 2027 women with a mean age of 71 years and baseline femoral neck T-score of approximately –2.1. He reported an absolute risk reduction of hip fractures by 1.2 % (CI .23-.99).

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was designed to examine effects of raloxifene on bone (23). Two groups of subjects were enrolled: 1) subjects with osteopenia and at least one moderate-severe or at least two mild vertebral fractures; 2) subjects with osteoporosis of the hip or spine. Primary endpoints included new vertebral fractures and BMD changes. Any non-vertebral fracture was a secondary endpoint. This study followed 7705 postmenopausal women (mean age 67 years) for three years. There was no significant difference between women taking raloxifene or placebo and the incidence of hip fractures. Of interest, the efficacy of reducing vertebral fractures was greater in women with a prevalent spine fracture. The number needed to treat (NNT) to prevent vertebral fractures was 42 in women with at least one vertebral fracture and 113 with no prior fracture.

Chesnut (62) reported the findings from the Prevent Recurrence of Osteoporotic Fracture Study. This study enrolled 1255 women with a mean age of about 68 years of which 80% had a prevalent vertebral fracture. Subjects received either placebo or one of 3 does of intranasal

calcitonin. There were very few hip fractures in this study and no significant overall reduction was seen.

How Long Should Bisphosphonates be Prescribed?

The prolonged biological activity of these agents has raised safety concerns and at the same time offers the possibility of therapeutic convenience and efficacy.

Bisphosphonates are analogues of pyrophosphate. They are resistant to enzymatic hydrolysis and are not metabolized. They are highly specific for bone and bind to exposed hydroxyapatite surfaces of bone remodeling sites where they inhibit resorption by decreasing the number and activity of osteoclasts (72). Some drug is released back to the circulation and is cleared by urinary excretion. Bisphosphonate is incorporated into newly formed bone and remains there until exposed once again during a new remodeling cycle. A newly activated osteoclast exposed to the previously deposited bisphosphonates inhibits bone resorption in the subsequent cycle of remodeling. The estimated terminal elimination half-life for alendronate is 10.5 years (73) and is 20 days for risedronate (74,75). Hence, because of their prolonged biologic effect, theoretical concerns have been raised that chronic administration could lead to impaired bone quality and fractures. Women starting therapy at 50 years of age could potentially use these agents for 30-40 years. We do not yet know what the impact this duration of therapy will have. It is known that at least seven years of bisphosphonate therapy appears to be safe with little or no evidence that poor quality bone is produced. In addition, a number of short-term studies have published the effect of combination therapy with bisphosphonates and other antiresorptive drugs with small additional increases in bone density but no evidence showing improved (or impaired) antifracture efficacy (76-80).

Yet, there are reports of low bone turnover and increased fracture risk in women (81). The combination of antiresorptive agents (a bisphosphonate and estrogen for example) has raised the most concern for excessive suppression of bone turnover resulting in "frozen bone" with accumulated microdamage and impaired bone material properties, thus rendering the bone at increased risk for fractures (80,82-84). These concerns have not been confirmed in clinical trials (85); however, there have been recent cases that support these concerns (Odvina, et al., personal communication).

On the other hand, the pharmacodynamic properties of bisphosphonates have led the FDA to approve weekly dosing of bisphosphonates (86). In addition, zoledronic acid, approved for use in hypercalcemia of malignancy, is being studied as a once a year IV administration in patients with osteoporosis (87). The prolonged half-life of bisphosphonates may also prove to offer the advantage of being able to be given at prolonged dosing intervals. For example, after a number of years of therapy it may be possible to withdraw therapy for a period of time, and then resume therapy if and when bone density falls or biochemical makers of resorption increase significantly. Tonino, et al. found that in 350 patients (mean age 63 with T-score below -2.5) who had taken alendronate for 5 years and subsequently monitored off therapy for 2 years had no significant decline in BMD at the spine or hip (88). There were small increases in urinary N-telopeptide (-73% from baseline at 5 years rising to -57.9% at 7 years) and serum bone specific

alkaline phosphatase (-55 at 5 years to -36.7% at 7 years), reflecting bone resorption and formation, respectively, but far below baseline values. Intermittent dosing of bisphosphonates is likely to be more successful compared to estrogens because of the prolonged biologic activity in contrast to estrogens where bone loss is accelerated and fracture protection wanes rapidly after discontinuation (66,80,81).

Summary

Over the past few years the availability of BMD testing and the number of options for both prevention and treatment of osteoporosis have greatly expanded. The US Preventive Services Task Force (USPSTF) has recently published screening guidelines for osteoporosis in postmenopausal women (91). The USPSTF recommends that women 65 years of age and older be screened routinely for osteoporosis. They also recommend screening for women at least 60 years of age who are at increased risk for osteoporotic fractures; this is a grade B recommendation. They made no recommendation for women younger than 60 years or for women 60 to 64 years who are not at increased risk for osteoporotic fractures (grade C recommendation).

Although BMD testing can identify patients at risk for fracture, clinicians need to be able to correctly interpret results. If at all possible, patients should be measured on the same machine (make and model). Currently, DXA scanning is the preferred method to measure BMD. Most patients should have measurements of both the spine and hip. The use of BMD in non-Caucasian female populations should be interpreted cautiously and the reference group should be identified. Patients with prevalent vertebral fractures should be particularly targeted for evaluation and treatment as they are at the highest risk for recurrent fractures; a number of clinical trials have shown more robust fracture reduction when these patients are treated. For screening purposes, measurement every 2 years for postmenopausal osteoporosis is adequate for most patients. For patients being treated, scanning every one to two years is appropriate if the intervention is likely to increase BMD in excess of the precision error of the device (multiplied by 2.8), generally an increase in excess of 3%. The most morbid outcome associated with osteoporosis is hip fracture. Unfortunately, pharmacological interventions are likely to play a limited role in preventing these events.

Although there are inconsistencies and challenges in our current diagnostic and therapeutic approach to managing patients with osteoporosis, the field is young. Just as ATP III management guidelines incorporate multiple variables to determine a patient's risk, a similar approach will evolve in osteoporosis management. Some have likened our current understanding of osteoporosis to that of hypertension or hyperlipidemia 30 years ago. As we develop ways to assess bone strength directly, we will be able to better assess fracture risk and evaluate the efficacy of medications in improving bone quality and in preventing fracture. In the end, we will need to develop strategies that prevent falls as well as those which will increase bone quality.

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