Prevention of fractures in the elderly

A review

Olof Johnell

Department of Orthopedics, Malmö General Hospital, Lund University, S-214 01 Malmö, Sweden
Tel + 46 40-33 10 00. Fax -33 62 00
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Definition of osteoporosis

The NIH consensus conference in 1991 defined osteoporosis as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Osteoporosis is defined as a disease and the risk factor for the disease is low bone mass and the clinical manifestation is a fragility fracture. This is analogous to hypertension, where cerebral vascular disease is the disease, blood pressure the risk factor and stroke the clinical end-point.

There are several ways of defining osteoporosis with the risk factor of bone mineral density. One way is to define a threshold, i.e., bone mineral density 2.5 SD below the peak bone mass at the age of 20–40; the WHO study group has suggested that –2.5 SD below peak bone mass is equivalent with the diagnosis of osteoporosis.. For an SD of 2.5 this would mean that one fifth of 50–80-year-old women in Sweden are at risk (Table 1). Another is to define osteoporosis as a change compared with the expected bone mass for that age and sex and thus select subjects for intervention among those below 1 SD of the mean with 17 percent at risk—this mainly for prognosis and prevention of osteoporosis (Table 1). A third way is to calculate the lifetime risk of a fracture based on age, sex and remaining life-expectancy (Melton et al. 1993).

Osteoporosis fractures—morbidity and mortality

The classic fragility fractures occur in the vertebra, the hip, and the distal end of the radius (Colles' fracture). Fractures of the proximal end of the humerus (low trauma), pelvis, lateral tibial condyle, and of the lower part of the femur (Bengnér 1987) can also be regarded as fragility fractures. As regards hip fracture, which has the highest residual morbidity, most studies have shown that only half of the patients had returned to their prefracture status after 1 year (Johnell 1993, Thorngren 1994). Most hip fractures occur at a mean age of 80 in women, and are naturally associated with morbidity and sociological problems, even before the fracture. The costs of hip fractures are also high, since the patients are hospitalized and operated on. In Sweden a fracture of the hip costs SEK 81,000 (Borgquist et al. 1991) for the first 4 months and SEK 150,000 for the first year (Sernbo and Johnell 1993), which is the same as the cost for a patient with stroke (SEK 160,000) (SBU report).

Moreover, fractures as a result of vertebral osteoporosis have a residual morbidity with pain and reduced quality of life. Scane et al. (1994), in the Nottingham Health Profile, found that men (mean age 65) had a 6–8 times worse outcome in some of the global scores. However, there are several vertebral fractures—deformities that are not associated with pain. Ettinger et al. (1992a), in a population-

Table 1. Fraction at risk of osteoporosis in Sweden defined as BMD 2.5 SD below young adults (mean of hip, neck, ward trochanter) or 1 SD below age matched controls, thousands

Age group	Population	No. at risk	
		2.5 SD below young adults	1 SD below age matched
20–29	590	0	
30–39	570	0	
40–49	620	10	
50–59	500	40	80
60–69	420	65	70
70–79	410	120	70
80–89	230	65	40
>50		290 19%	260 17%

based prevalence study of close to 3,000 women, found that vertebral deformities with a decreased ratio of more than 4 SD had a 2–3 times higher risk of moderate-to-severe back problems.

Determinants of osteoporosis fractures

Fractures can be caused by skeletal changes, such as low bone mass, rearranged spatial orientation of bone, changed turnover and deterioration in quality of bone. Fractures are also caused by extraskeletal factors, such as falls, poor neuromuscular coordination, size of the soft tissue cushion and the physical environment, e.g., hard surfaces.

The most important cause of osteoporosis fractures seems to be decreased bone mass. Techniques for measurement of bone mass have improved substantially during the last decades (Nilsson et al. 1990). Single photon absorptiometry (SPA) was first used but has been replaced by single photon x-ray (SPX), where the isotope is exchanged for a roentgen ray tube which is stable and permits a precision of 1 percent. For the measurement of the axial skeleton, spine and hip, dual photon absorptiometry (DPA) must be used. In recent years, this has been replaced by dual roentgen absorptiometry (DEXA), where a roentgen tube is used instead of an isotope. With this equipment, one can measure any region of the body as well as the composition of the body. Quantitative computed tomography (QCT) is also used in some centers. The latest development is ultrasound measurement, which evaluates both bone mass and elasticity from the attenuation and speed of sound. Hitherto, few prospective data have been published on the ability of this method to predict fractures (Porter et al. 1990).

With modern equipment, bone mineral measurements have a precision of 1 percent. This means that a 2.8 percent change is needed to ensure statistical significance. In a woman, 1–2 years are required for such a change, thus re-measurements should not be done before this time.

How well can bone mineral measurements predict later fractures? Several prospective studies have now shown that bone mineral measurements can predict fractures. To compare the various methods one has to calculate a 1 SD decrease in the mean. The relative risk of having a fracture with a 1 SD decrease in bone mass is between 2 and 4 (Wasnich et al. 1987, Hui et al. 1988, Cummings et al. 1993, Gärdsell et al. 1993, Melton et al. 1993, Nguyen et al. 1993). The predictive ability of the latest data is a RR of 1.6–3 for a 1 SD decrease. In several studies a 1 SD decrease means a 15–20 percent decrease in the bone mass. The question is: What equipment and site should we use? It would appear that the ability to predict all kinds of fractures at various measuring sites, including the forearm, spine and hip seems to be equally good. However, for a hip fracture, data have now been presented that measurements of the hip have a better predictive ability than those of the spine or forearm (Cummings et al. 1993). The predictive ability is good—much better than that of cholesterol—a 1 SD increase in the cholesterol level has a relative risk of 1.3 for coronary heart disease (CHD) later in life—and is equal to a 1 SD change in scintimetry 2 weeks after a hip fracture in predicting failures after this fracture. Recent studies have also shown that one can predict hip fractures and other non-spinal fractures, even at 80 years of age for a 4-year period (Nevitt et al. 1994). In conclusion, bone mineral measurements can predict fractures well and therefore can identify patients at risk for fractures, even at higher ages.

Roentgen of the spine

To define vertebral fractures—deformations—a new technique has been developed where 6 points are marked on each vertebra and anteroposterior, mid-posterior and two posterior ratios above and below are calculated. In a study from Hawaii, Ross et al. (1991) showed that, for a person with a baseline fracture deformation, the risk of sustaining a non-spinal fracture is 4 times higher. Vertebral deformities may in future be an indication for intervention, with or without a bone mineral measurement.

Biochemical markers

During the last decade new effective markers have been found. The osteoblasts produce several substances that can be used as markers. Breakdown products of bone by osteoclasts have also been used as resorption markers. The most commonly used markers are osteocalcin for bone formation and pyridinoline for bone resorption. In the coming years, new markers will undoubtedly become available that need to be validated. The advantage of a marker is that one can monitor the effect of a treatment much more quickly than with a bone mineral measurement. Some reports show that the effects of certain anti-resorptive drugs are better if patients with a high turnover are selected (a high turnover means that an individual has increased formation and resorption).

Table 2. Factors associated with increased risk of osteoporosis fractures

Caucasian race
Age
Early menopause
Low muscle strength
Low calcium intake
Prolonged immobilization or inactivity
Smoking
Alcohol abuse
Low body mass index
Positive family history
Previous fragility fracture
Certain diseases
Various drugs—glucocorticoids

No marker is available at present that can be used for the diagnosis of osteoporosis.

Balance and body sway

Balance also affects the risk of fracture. Nguyen et al. (1993) recently showed that increased body sway increases the risk of future fractures independently of bone mineral density. A 1 SD change in body sway had a relative risk of 2—which was fairly close to the bone mineral density prediction (RR 2.40) in that study.

Other risk factors

There are several other risk factors, including factors for secondary osteoporosis, such as body weight, low calcium intake, etc. (Table 2). It is probably useful to add these to the bone mineral density to enhance the prediction of fractures in groups or individuals.

Interventions

The first intervention is to change lifestyle factors. Physical activity, smoking, excessive alcohol intake, etc., may be possible to change. This is the first advice and should probably be the only intervention in those with only a minor reduction in bone mass. However, there are no major prospective studies to prove this. After changes are made in lifestyle, additional intervention may be considered. The next intervention is drugs, and estrogen is the first choice. It is approved for this purpose in most countries. Many investigations show that bone mass increases with estrogen medication. In 20 recent prospective and randomized studies, a difference of approximately 3 percent a year compared to a control group was found (Nachtigall et al. 1979, Genant et al. 1982, Sanvig Christensen et al. 1982, Christiansen and Rödbro 1984, Linday et al. 1984, Jensen et al. 1987, Riis et al. 1987, Munk-Jensen et al. 1988, Riis et al. 1988, Savvas et al. 1988, Adami et al. 1989, Ribot et al. 1989, Hirvonen et al. 1990, Stevenson et al. 1990, Gallagher et al. 1991, McNeeley et al. 1991, Casteol-Branco et al. 1992, Ettinger et al. 1992b, Lufkin et al. 1992, Field et al. 1993) (Table 3). However, all except one of these investigators (Lufkin et al. 1992) have started the treatment at menopause and, in most studies, subjects have not been selected because of a low bone mass. In some studies, biochemical markers show that estrogen produces its effects by reducing the turnover of bone in that both bone formation, marked by osteocalcin, and bone resorption, marked by hydroxyproline, are reduced up to 40 percent during the first year (Table 3). The longest of these studies was a 10-year controlled trial (Nachtigall et al. 1979) showing a 15 percent bone mass increase. Thus estrogen treatment for 5–10 years can be expected to increase the bone mass by 10–15 percent which would reduce the risk of sustaining a hip fracture by one half. There is also

Table 3. Effect of estrogen treatment, number of studies, mean percentage difference from controls, *SD*

Treatment time (yr)	N	SPA (%)	N	Osteocalcin (%)	N	Hydroxyproline (%)
0.5			3	–24 *18*	5	–31 *20*
1	3	3.0 *2.0*	4	–45 *25*	7	–45 *18*
2	6	7.5 *3.0*	2	–46 *20*	7	–40 *12*
3	1	7.0				
4	2	10.0 *0.2*				
10	1	14.5				
per year	13	3.0 *1.5*				

SPA Single photon absorptiometry

Table 4. Postmenopausal estrogen treatment and hip fracture

	RR ever/never	Duration yrs	RR
Case control			
Hutchinson et al. 1979	0.2	>5	0.02
Weiss et al. 1980	0.4	>10	0.5
Johnson and Specht 1981	0.7		
Paganini-Hill et al. 1981	0.7	>5	0.4
Kreiger et al. 1982	0.4		
Williams et al. 1982	0.4		
Kanis et al. 1992	0.6		
Cohort			
Hammond et al. 1979	0.5		
Ettinger et al. 1985	0.4		
Kiel et al. 1987	0.6		
Naessén et al. 1990	0.8		
Paganini-Hill et al. 1991	1.0	>15	0.9

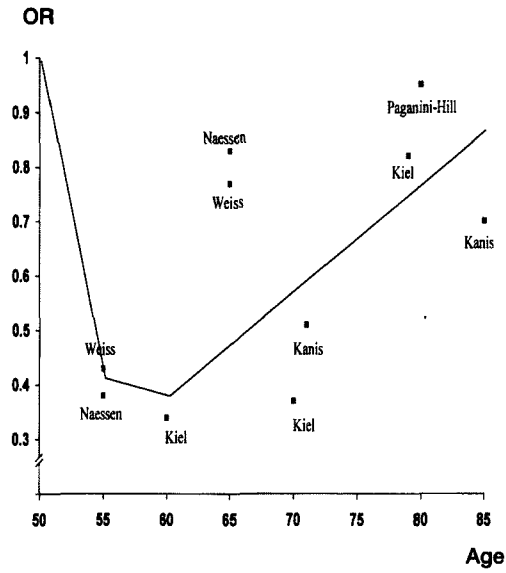

Figure 1. Plot of some studies where treatment starts at 50 using estrogen for 5–10 years with an odds ratio (OR) of less than 0.5 during the years following treatment but OR 0.7–0.8 or even higher 30 years after the menopause (Weiss et al. 1980, Kiel et al. 1987, Naessén et al. 1990, Paganini-Hill et al. 1991, Kanis et al. 1992).

one prospectively randomized study on estrogen with vertebral fractures or deformities as the end-point (Lufkin et al. 1992). Patients were selected because of osteoporosis (low bone mass and vertebral fracture, mean age 65) and there was an increase in bone mass and a lowering of the vertebral deformations by 70 percent. However, one report from the Framingham study (Felsen et al. 1993) shows that those who started estrogen at menopause had no difference in bone mass at the age of 80, compared to controls. Thus, there was a tendency to a decreased effect from the time of drug cessation. A number of epidemiological studies have examined estrogen users vs non-users and hip fracture incidence (Hammond et al. 1979, Hutchinson et al. 1979, Weiss et al. 1980, Johnson and Specht 1981, Paganini-Hill et al. 1981, Kreiger et al. 1982, Williams et al. 1982, Ettinger et al. 1985, Kiel et al. 1987, Naessén et al. 1990, Paganini-Hill et al. 1991, Kanis et al. 1992) (Table 4). The protective effect in most of these epidemiological studies is 0.5–0.8. As judged by these studies, the effect seems to be less as time passes after the estrogen consumption period. Some studies have tried to take this into account and in Figure 1 where treatment starts at 50 and includes estrogen for 5–10 years, data from Kiel et al. (1987), Naessén et al. (1990), Paganini-Hill et al. (1991) and Kanis et al. (1992) show an odds ratio of less than 0.5 during the years following the consumption and it may be even 0.7–0.8 30 years after the menopause. These data have also been used for modeling by Johnell et al. (1993), who estimated a difference in the number of hip fractures predicted if the effect gradually decreased after the drugs were discontinued as compared to a constant effect over the years.

In the MEDOS study (Kanis et al. 1992), there was also a protective effect in women older than 80, but it was not significant. The cost of a 1-year treatment in Sweden is approximately SEK 600–1600.

Other drug treatments

Calcitonin, mainly as injections, is approved for treatment of osteoporosis in several countries in Europe. Several studies have shown an increased bone mass after calcitonin treatment and 3 studies with fracture end-points showed fracture reduction (Peyron et al. 1990, Kanis et al. 1992, Overgaard et al. 1992). It is still debated whether to treat intermittently or continuously and, if intermittently, at which intervals. The cost of calcitonin is high: for 6 months' treatment SEK 4600.

Bisphosphonates: Bisphosphonate is an interesting substance, since it reduces bone resorption. Some studies on long-term treatment with bisphosphonates show a positive effect on bone mass and on vertebral deformations (Storm et al. 1990, Watts et al. 1990) (Table 5). However, fracture data are still lacking. Earlier studies with first-generation bisphosphonates have used 2 weeks of treatment every 3 months. The newest generations of bisphosphonates are meant for

Table 5. Prospective studies and fractures

Ref.	Selection (n)	Age	Treatment	Fractures/1000 women		RR
				Treatment	Control	
Watts et al. 1990	V (429)	65	B	30 (V)	63	0.48
	only low BMD	>65	B	42 (V)	133	0.32
Storm et al. 1990	V (66)	68	B	60 (V)	540	0.11
Overgaard et al. 1992	low BMD (208)	70	C	32 (A)	100	0.32
Chapuy et al. 1992	(3270)	84	D	39 (H)	66	0.59
Lufkin et al. 1992	low BMD + V (75)	65	E	230 (V)	580	0.39
Lauritzen et al. 1993	(497)	84 (W)	H	46 (H)	98	0.46
		82 (M)	H	14 (H)	46	0.29

Selection and type of fractures
A All
H Hip
V Vertebral

Treatment
B Bisphosphonates
C Calcitonin
D Vitamin-D
E Estrogen
H Hip protector, external

continuous use in a lower dose. Data within the next years will show the effect of this treatment.

Anabolic steroids: Several reports have shown a positive effect on bone mass and one study had an almost significant fracture reduction of 40 percent (Kanis et al. 1992).

Vitamin D: Two prospective randomized studies have indicated that vitamin D had a positive effect on fractures. One is the study by Tilyard et al. (1992) with a potent vitamin D preparation and the other is by Chapuy et al. (1994) who examined the results of treatment with vitamin D 800 IU and a calcium supplement of 1.2 g. They showed that after 3 years of treatment of patients with a mean age of 82, hip fractures were reduced by 40 percent indicating that this might be an alternative in the very elderly.

Fluoride has also been tried. However, fluoride has a very narrow therapeutic range (Riggs et al. 1994) and the effect on bone quality is uncertain.

Parathyroid hormone, growth hormone and *growth factors* have also been tested.

Table 5 shows results with fracture end-points for prospective, randomized trials (Storm et al. 1990, Watts et al. 1990, Chapuy et al. 1992, Lufkin et al. 1992, Overgaard et al. 1992, Lauritzen et al. 1993). Watts et al. and Storm et al. gave bisphosphonates and included patients above 65 years, mostly with vertebral fractures. They both found a protective effect on the number of vertebral fractures during a 2-year treatment period. Overgaard et al. (1992) studied patients who had been given intranasal calcitonin during a 2-year period and found a significant reduction in all clinical fractures. Chapuy et al.'s (1992) initial study during the first 18 months is presented in Table 5. They performed a follow-up over a total of 36 months (3 years) with a treatment consisting of 1.2 g calcium, 800 IU cholecalciferol-vitamin D_2. They found reductions in the number of hip fractures (Chapuy et al. 1994) (29 percent) and in all non-vertebral fractures (24 percent) in the treatment group. Lufkin et al. (1992) treated women with transdermal estrogen who had a mean age of 65, all of whom had osteoporosis. After 1 year of treatment, they found a significant reduction in the number of vertebral fractures.

Another method of preventing hip fractures was applied by Lauritzen et al. (1993). They used external padded hip-protectors in nursing home patients and in the general population and found during an 11-month study period a reduction in the number of hip fractures in those who had used the protector. In women, the RR was 0.5 and in men 0.3. This may be an alternative method for the prevention of hip fractures in the elderly.

Guidelines

Screening: As stated previously, bone mineral density measurement has a good predictive effect, but what does it mean in a screening setting? Data from the SOF study (Nevitt et al. 1994), with 10,000 women, mean age 71, and followed prospectively show that subjects in the lowest bone mass quartile, have an almost 4 times higher risk of hip fracture than the rest. These data are applicable to Sweden, where the lifetime expectancy of a patient with hip fracture after the age of 50 is 15 percent. If we screen 1,000 individuals, there would be 250 in the lowest quartile of BMC and among these there would be 84

Table 6. Modelled screening with BMC/D of 1000 women, older than 50, with 15% lifetime risk of hip fracture (RR 3.8)

BMD measurement (n 1000)	Distribution	Hip fractures
Lowest quartile	250	84
The rest	750	66
Total	1000	150

Table 7. Modelled effect of treatment of lowest BMC/D quartile of 1000 cases (RR 3.8)

Risk of hip fracture in treatment group	Untreated	Treated	Percent reduction of hip fractures
15% lifetime risk	150 (84+66)		
70% reduction		91 (25+66)	39
50% reduction		108 (42+66)	28
20% reduction		133 (67+66)	11

Table 8. Modelled screening with BMC/D of 1000 women, older than 50, with 15% lifetime risk of hip fracture (RR 3.8)

BMD measurement (n 1000)	Distribution	Hip fractures
–1 SD	170	68
The rest	830	82
Total	1000	150

Table 9. Modelled effect of treatment of lowest BMC/D quartile of 1000 cases (RR 3.8)

Risk of hip fracture in treatment group	Untreated	Treated	Percent reduction of hip fractures
15% lifetime risk	150 (84+66)		
50% reduction		108 (42+66)	28
+ compliance 50%		129 (63+66)	14
+ compliance 90%		111 (47+64)	26

Table 10. Modelled effect of treatment during treatment of lowest BMC/D quartile of 1000 cases, 77 years old (RR 3.8)

Risk of hip fracture in treatment group	Untreated	Treated	Percent reduction of hip fractures
1–2% in 3 years	45 (26+19)		
70% reduction		27 (8+19)	40
50% reduction		32 (13+19)	29
20% reduction		40 (21+19)	11

Table 11. Modelled effect of treatment of lowest BMC/D quartile of 1000 cases (RR 3.8) asuming that they constitute half of the patients seen in the clinic (i.e. 50% treated)

Risk of hip fracture in treatment group	Untreated	Treated	Percent reduction of hip fractures
15% lifetime risk	214 (171+43)		
70% reduction		94 (51+43)	56
50% reduction		128 (86+43)	40
20% reduction		179 (137+43)	16

hip fractures. In the 750 who will not be treated, there will be another 66 hip fractures. If we start treating those in the lowest quartile with drugs, I have modeled three different effects from the data in Table 6, a 70, a 50, and a 20 percent reduction in fractures (Table 7). The overall number of hip fractures will be reduced by 39, 28, and 11 percent, respectively, because among the 750 who will not be treated, hip fractures will still occur. Another problem with a lifetime risk of 15 percent is that, among those treated, only 1 in every 4 will have a hip fracture. If we instead select those in the group 1 SD below the mean and estimate their risk to be 4 times higher than the rest (Table 8), the prediction of fractures will be more accurate (68 fractures among the 170). 830 of the 1,000 screened subjects will not be treated, but they will have 82 hip fractures. Another problem is that compliance for estrogen in screening samples has been fairly low (Stevenson 1992) and, if this is taken into account, the effect is further reduced (Table 9). So long as the compliance is low, screening is probably not effective (Johnell 1992).

A more critical and limited way to look at this question is to study only the treatment period. If we in Sweden start treating a 77-year old woman, she will run a 1–2 percent yearly risk of having a hip fracture during the next 3 years. This means that 45 fractures will occur in 1,000 women during that period (Table 10).

Patient-doctor relationship

This relationship differs from that in screening since most of the patients who are examined have a much higher risk of osteoporosis than those in the general population. If one makes the same calculation as that for the screening, one can assume that every other patient or 2 out of 3 will have a bone mineral density value less than the intervention threshold and, with these options, the effect of the bone mineral measurements and the number of hip fractures prevented in the clinical setting are much greater (Table 11) than in the screening model and therefore the compliance would certainly be higher.

Conclusion

Data now available show convincingly that measurements of bone mineral density can predict hip fractures as well as other fractures and be used as a clinical tool. A previous fracture can also predict later fractures. Other data demonstrate that several types of treatment regimens reduce the fracture rate. It seems to be worthwhile to treat patients today in a patient-doctor relationship and perhaps later also in a screening setting, if the compliance problem can be solved.

For those with only minor reduction in bone mass, lifestyle changes are probably enough and a new measurement can be made within 2 years. For those with osteoporosis, estrogen is the first choice. If the woman has an intact uterus, gestagen should be added. The treatment should continue for 5–10 years—in some cases even longer as a prophylactic measurement. As a treatment for osteoporosis when you have had a fracture or are 2.5 SD below the mean after the age of 75, estrogen could perhaps be considered. Other alternatives are calcitonin and bisphosphonates. The duration of use is still debated, but 3–5 years is suggested. Another alternative could be anabolic steroids, e.g., to hip fracture patients. Elderly people in nursing homes can be given vitamin D 400–800 IU and a calcium supplement of about 1 g. In some patients, nursing-home hip protectors may also be considered. Special cases are those who start taking glucocorticoids in fairly high doses for more than 6 months. Here prevention should be considered from the start of treatment.

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