Special Topic: Risk Factors

Risk Factors For Osteoporosis and Associated Fractures

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Synopsis

Established risk factors for osteoporosis and associated fractures are increasing age, female sex, white race, removal of the ovaries at an early age, prolonged immobility, and prolonged use of corticosteroids. Obesity and use of estrogen replacement therapy are protective. Factors that probably or possibly increase risk in postmenopausal white women include a low calcium intake, cigarette smoking, and, at least for hip fractures, use of long half-life psychotrophic drugs and heavy alcohol consumption. Factors probably or possibly associated with a decreased risk include ingestion of vitamin D and its metabolites, fluoride levels of 2 ppm or more in drinking water, moderate physical activity, pregnancies and breast feeding, use of thiazide diuretics, and progestogens. Some evidence suggests that calcium intake and physical activity at young ages may be important determinants of peak bone mass. Few studies have been undertaken in males and blacks, although at least some risk factors in males may be similar to those in females. Preventive efforts may be aimed at increasing peak bone mass at young ages, preventing bone loss in postmenopausal women, and preventing fractures and their adverse consequences in older people with osteoporosis.

MOST STUDIES of risk factors for osteoporosis and associated fractures have been undertaken in white, postmenopausal women. This paper will therefore focus mostly on risk factors in this group. However, to the extent that data are available, the last section will cover other topics of special interest, including determinants of peak bone mass in young adults, bone mass in young people with anorexia nervosa, and risk factors in men and in blacks.

Osteoporosis and Osteoporotic Fractures In White Women

Demographic characteristics. The demographic factors most strongly associated with osteoporosis and osteoporotic fractures are increasing age, female sex, and white race. Figure 1 shows that after about age 50, incidence rates for hip fracture increase rapidly with age among white women *(1,2)*. In the early sixties, the incidence rate is around 2 per 1,000 per year, whereas at age 85 and older, the incidence rate is greater than 3 percent per year. Incidence rates for hip fracture also increase steeply with age in older men, but at any given age above 50 years, the incidence rate in white women is slightly more than twice that in white men; furthermore, at all ages, bone density is greater in men than in women *(3,4)*.

A steep increase in hip fracture incidence rates with age also occurs in black women, but the age-specific incidence rates for white women are a little more than twice those for black women at any given age *(2)*. Greater bone density and lower fracture rates have been found in black women than in white women at all sites studied to date *(2-11)*.

Oophorectomy. A particularly rapid rate of bone loss occurs in women in their fifties, suggesting that menopause precipitates this period of rapid rate of bone loss. Early removal of the ovaries is also associated with an earlier onset of rapid bone loss *(12,13)*.

Estrogen replacement therapy. The above observations suggest that estrogen replacement therapy (ERT) may protect against osteoporosis and its associated fractures. In fact, studies undertaken to date show that estrogen does preserve bone mass in all sites studies, as long as it is used *(14-22)*. After administration of estrogen ceases, bone mass is lost at a rate similar to that observed immediately after the menopause in women who were not treated with

estrogen *(22,23)*. The longer ERT is used, the lower the risk for the clinically most significant consequence of osteoporosis, hip fracture *(24-27)*. The relative risk of fracture of the hip or lower forearm was 1.0, 0.8, 0.9, 0.4, and 0.5 when postmenopausal ERT was used for 0 or < 1, 1-2, 3-5, 6-9, or > 10 years, respectively *(24)*.

Obesity. Most endogenous estrogen in postmenopausal women comes from the conversion from its androgen precursor in adipose tissue; the greater the amount of adipose tissue, the greater the amount of estrogen *(28)*. Thus, obese women would be expected to have a lower risk for osteoporosis, and its associated fractures, than thin women. Table 1 shows results from a study in which body weight of women with hip fractures was compared with the body weight of two groups of women in the same age range without hip fracture *(25)*. In each of the age groups considered, the body weight of those with hip fracture was considerably below that of the comparison patients. Obesity has been associated with greater bone density and fewer fractures in all sites studied to date *(22-27,29-40)*.

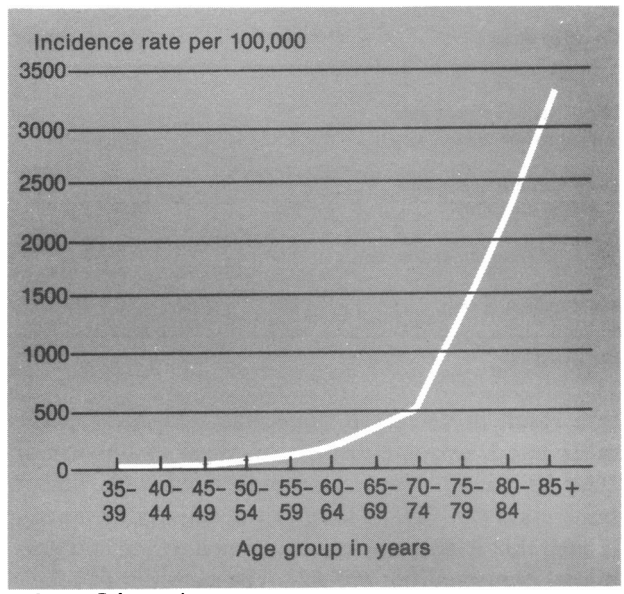
Diet. Calcium, fluoride, and vitamin D have been the most extensively studied dietary factors. Vitamin D metabolites are known to affect calcium absorption, but to date results of the effect of vitamin D and its metabolites on bone mass have been inconsistent *(12,15,17,31,32,41-53)*, and this is an area of active research at present. Some studies suggest that residents of communities with > 2 ppm fluoride in drinking water have lower rates of vertebral fractures *(54)* and mortality from falls *(11)* and greater radial and spinal bone mass *(54,55)* than persons living in communities with low levels of fluoride. With one exception *(56)*, however, no studies have shown a protective effect of fluoride at the 1 ppm level *(11,55,57-59)*. Other differences between communities with high and low levels of fluoride could account for the variations in rates, however, so that this evidence is considered suggestive but not definitive.

The greatest interest in recent years has focused on calcium consumption. Epidemiologic studies that have compared dietary intake of calcium of women with osteoporotic fractures to that of women of the same age without such fractures, or dietary calcium intake of women with low bone density to that of women with higher bone density, have generally shown no difference between the cases and controls, or at most a very slight difference in that the cases have, on the average, slightly less dietary calcium than the controls *(32,60-64)*. Measurement of dietary calcium intake is difficult, so that it is impossible to know whether the failure to find a protective effect means that there really is none or that, because of the difficulty, an effect cannot be detected. Also, diet during childhood and adolescence may be more critical than diet in the adult years. *(65)*.

A few randomized and nonrandomized trials of the effect of calcium supplementation have been undertaken in postmenopausal women. Results of these trials vary somewhat, but taken as a whole they indicate that calcium supplementation somewhat retards loss of cortical bone mass, but not trabecular bone, and that the protective effect of calcium is considerably less than that of estrogen *(17,18,49,66-73)*.

Physical activity. Physical activity has also been the subject of a great deal of interest. There is general agreement that prolonged inactivity and immobiliza-

Age specific incidence rates per 100,000 for hip fracture among residents of Rochester, MN



Source: Reference 1.

Table 1. Mean weight, in pounds, of hip fracture cases and two control groups, by age[1]

Age in years	Cases		Trauma controls		Nontrauma controls	
	Number	Mean	Number	Mean	Number	Mean
49-59 ...	22	136.7	36	144.6	416	149.3
60-64 ...	22	131.0	21	152.1	150	141.8
65-74 ...	50	125.9	26	142.5	230	141.3

[1]Reference *(25)*.

Table 2. Relative risk of hip fracture among users of four classes of psychotrophic drugs within 30 days of index date[1]

Class of drug	Relative risk	95 percent confidence interval
Short half-life hypnotics/ anxiolytics only	1.1	0.8 - 1.6
Long half-life hypnotics/ anxiolytics only	1.8	1.3 - 2.4
Tricyclic antidepressants only	1.9	1.3 - 2.8
Antipsychotics only	2.0	1.6 - 2.6

[1]Reference *(89)*.

tion result in decreased bone mass *(73-76)*. On the other hand, extreme degrees of physical activity, at least in young people, are associated with higher bone mass *(77-79)*, as long as the activity in women is such that it does not result in amenorrhea and hormonal abnormalities *(80-82)*. The question of greatest concern is whether the moderate physical activity in which older people might engage affects bone mass and risk of osteoporotic fractures. One study *(27)* found that the risk for hip fracture decreases as reported physical activity level increases; nonrandomized trials have also shown some protection against bone loss *(83-85)*. However, observational studies are difficult to interpret because people who are physically active may have other lifestyle characteristics that affect their risk for osteoporosis. They may have more calcium in their diet, they may not smoke or drink, and they may be physically healthy and unlikely to fall and incur hip fractures. Thus randomized trials are needed of the effect of physical activity on bone mass and fractures. A few randomized trials are in progress. Preliminary results indicate only modest or no protection against loss of bone mass *(86)*. However, physical activity at young ages, when bones are rapidly growing, may be more critical than physical activity at older ages.

Cigarette smoking and alcohol consumption. Studies have shown that women who smoke cigarettes have a greater risk of hip, vertebral, and Colles' fractures, and lower cortical bone mass, than women who do not smoke *(27,31,35,40,87,88)*. One study *(27)* found that the relative risk (adjusted for estrogen use and ovarian status) for hip fracture was 1.0, 1.1, and 2.0 when 0, 1-10, or > 11 cigarettes per day, respectively, were smoked by postmenopausal women. There is also a question of whether it is the cigarette smoking or other lifestyle characteristics of smokers that is associated with loss of bone mass and fractures. Estrogen metabolism does appear to be different in smokers from nonsmokers *(88)*, thus making an association between smoking and bone mass biologically plausible.

Some studies show that alcohol consumption is associated with risk for hip fracture *(26,27)*. For example, Paganini et al. *(27)* found that the relative risk (adjusted for estrogen use and ovarian status) for hip fracture was 1.0, 1.4, and 1.9 when 0, 1-7, or > 8 "shots" per week, respectively, were drunk by women after menopause. However, another study relating alcohol use to bone density showed no association *(15)*. Thus, alcohol consumption may increase the risk for falls, but have little effect on bone density.

Use of psychotrophic drugs. Table 2 shows results from a recent study relating psychotrophic drug use to hip fractures *(89)*. Drugs with a long half-life, but not those with a short half-life, were associated with an increased risk for hip fracture. The mechanism for this association is likely to be related to increased risk for falling.

Summary of Risk Factors in White Women

In summary, increasing age, female sex, white race, oophorectomy, prolonged immobility, and prolonged corticosteroid use *(90-92)* are associated with an increased risk for osteoporosis and associated fractures. Obesity and ERT are protective, at least for as long as the ERT is given.

Other factors probably or possibly associated with osteoporosis and risk of osteoporotic fractures are low calcium intake, cigarette smoking, use of long half-life psychotrophic drugs (at least for hip fracture), and heavy alcohol consumption (at least for hip fracture). On the other hand, several factors probably or possibly associated with a decreased risk for osteoporosis and associated fractures are ingestion of vitamin D and its metabolites, fluoride levels of 2 ppm or more in drinking water, moderate physical activity, pregnancies and breast feeding *(25,29-31,40,42,93)*, use of thiazide diuretics *(94-97)*, and progestogens, either alone or in addition to estrogens *(22,98-100)*. Studies of these probable or possible risk factors are either too few in number, or their results are too conflicting for definitive conclusions to be reached.

Strategies for Prevention

What does all of this tell us about possible strategies for prevention? Opportunities for preventive

efforts exist at several stages of life—childhood, adolescence, and early adult life, before peak bone mass is reached, are all such opportunities. Those people with higher levels of peak bone mass should be that much better off when they start losing bone mass, and it will take them longer to reach the threshold at which fractures will be likely to occur. Thus, some studies, discussed below, are focusing on determinants of peak bone mass.

During the early postmenopausal years, one strategy is to try to maintain bone mass in all women. At present, the only (known) way to do this is through estrogen administration. Another strategy is to screen for women who are fast losers of bone mass, or for women who have relatively low bone mass in their early postmenopausal years, and initiate prophylactic measures in these women. This is a controversial area that will be discussed in other papers.

Finally, in the older adult years, what can we recommend for women who already have osteoporosis? In addition to therapeutic measures to be discussed in other papers, one strategy is to try to prevent the most serious consequence of osteoporosis in these women, hip fracture, by reducing the likelihood of falls. This strategy has resulted in the initiation of several studies to identify risk factors for falls. Furthermore, among those who suffer fractures, some people recover adequately, while others deteriorate rapidly. Thus, a final strategy is to prevent adverse consequences, and maximize the chances of a good outcome, in those women who have suffered a fracture.

Other Areas of Interest

Determinants of peak bone mass. Insufficient data exist to reach firm conclusions about determinants of peak bone mass. However, a few studies have indicated that calcium intake *(65,101,102)* and physical activity *(101)* at young ages affect peak bone mass. Oral contraceptive use may at least be associated with increased radial cortical bone mass *(101,103)*. The role of other potential determinants of peak bone mass, such as pregnancies, breast feeding, beverage consumption, body build, and age at menarche have not been studied sufficiently to warrant even tentative conclusions.

Anorexia nervosa. The few studies that have been done in young women with anorexia nervosa suggest that bone density is lower in these women than other women of equivalent age *(104,105)*. One study *(104)* divided those with anorexia nervosa into those who were physically active and those who were not; those with anorexia nervosa who had little physical activity had low bone density, whereas those who were physically active tended to have bone density similar to control women without anorexia nervosa. Additional, larger studies of this issue are needed.

'Few studies have been undertaken in males and blacks, although at least some risk factors in males may be similar to those in females.'

Males. Only two case-control studies of hip fracture in men have been reported *(106,107)*, and they have identified the following risk factors: alcohol use, cigarette smoking, thinness, hypogonadism, corticosteroid use, previous gastrectomy, and neurological disorders that predispose to falling. Thus, some risk factors in men may be similar to those in women. However, more research on osteoporosis and associated fractures in men is needed.

Blacks. To date, no studies have apparently been published on risk factors for osteoporosis and osteoporotic fractures in blacks. However, studies of both bone density and hip fractures in black women have been started. As mentioned earlier, bone density is greater in blacks than whites, and several reasons for this difference have been hypothesized. Since bone mass is greater in blacks than whites at all ages, including the very young *(108)*, a genetic influence on bone mass has been postulated. Obesity is more prevalent in older black women than in white women *(109)*, and this condition could account for a lower risk. Diet and physical activity may differ between blacks and whites, particularly at young ages. Some evidence indicates that vitamin D metabolism differs in blacks and whites *(110)*. Other life-style characteristics could also account for the difference in risk.

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