Review articles

Prevention of osteoporotic fractures—should orthopedic surgeons care?

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There is evidence indicating that the number of hip fractures in Europe and the United States will roughly double by the year 2050. The number of hip fractures in Latin America and Asia will increase even further. The prognoses suggest that the number of hip fractures occurring in the world each year will rise from 1.7 million in 1990 to 6.3 million by 2050 (Obrant et al. 1989, Cooper et al. 1992). Facing a new millennium, how should we orthopedic surgeons act on this knowledge?

The efficacy of non-pharmacological and pharmacological treatment for osteoporosis or fracture prevention has recently been established in randomized, prospective trials (see below). So then, if there are treatment regimens that have proved to be efficient in large, prospective, blind studies, why should not orthopedic surgeons use these data for the benefit of our patients before or after they have sustained osteoporosis fractures? Treatment after a newly sustained fracture may also be cost-effective, since not only the bone mass but also recently sustained fractures are independent risk factors for future fractures (Cummings et al. 1995, Åkesson et al. 1995).

This communication reviews our present knowledge on this matter. I have chosen to make a critical review of prospective studies only. Some personal view points are also given on whom to treat, when to treat and who should be responsible for treating.

Non-pharmacological treatment

Physical activity

Cross-sectional studies have generally shown that active athletes have about 10% higher bone mass than non-exercising controls. In a few randomized, longitudinal studies on elderly women, the differences were also smaller, but there was a positive effect on bone mass of physical activity (Krölner et al. 1983, Chow et al. 1987, Simkin et al. 1987). There is thus evidence that in postmenopausal, osteoporotic women up to the age of 70, the trabecular bone mass increases or at least remains at the same level after an increase in physical activity.

Hip protectors

It is evident that regimens intended to reduce the number of falls will reduce the number of fractures. It has also been convincingly shown that the use of hip protectors reduces the number of hip fractures in individuals prone to falling, such as very elderly, institutionalized persons, with impaired walking capacity (Lauritzen et al. 1993, Ekman et al. 1997). Such hip protectors are sewn into the underwear to cover the hips, so that they cushion them in the event of a fall. One problem when prescribing such protectors is a possible violation of the integrity of the old and senile individual, who is at greatest risk of falling. In younger individuals, compliance may be a problem.

Pharmacological treatment

Calcium and vitamin D supplementation

Several randomized studies have shown that bone loss can be retarded, stopped or even reversed by giving elderly women calcium supplementation (Dawson-Hughes et al. 1990, Prince et al. 1991, Reid et al. 1993, Prince et al. 1995, Reid et al. 1995). There are no sufficiently large prospective studies showing a possible fracture-preventing effect of calcium. In only two studies, with 78 and 93 women, respectively, have attempts been made to demonstrate a fracture-preventive effect of calcium supplementation (Chevalley et al. 1994, Reid et al. 1995). Both studies were far too small to show any statistically significant ef-

fect of calcium supplementation, at least if individuals with fractures were to be counted. In an attempt to solve this power problem, "fracture rate" has frequently been used when comparing treatment groups with controls. This parameter counts the number of fractures per patient-year instead of the individuals with fracture. Windeler and Lange (1995) have pointed out that "The counting of events instead of patients, although used in papers published in journals of high scientific reputation, is merely suitable for a chapter in methodological errors in medical research".

The daily recommended calcium intake varies considerably from country to country (Schaafsma 1992, NIH 1994). It is evident from the above that giving calcium supplementation in food is beneficial for bone mass, but we do not know with certainty whether it also reduces the risk of fracture.

Vitamin D is necessary for normal mineralization of the skeleton and for absorption of calcium in the gut. Vitamin D deficiency leads to osteomalacia. Vitamin D_3 is synthesized in the skin when exposed to sun. Moreove, dairy products and fat fish contain vitamin D. Elderly people, who are not able to go outdoors and are to some degree perhaps malnourished, are therefore at great risk of becoming vitamin D-deficient (Ooms et al. 1994). Lips et al. (1996) analyzed the effect on osteoporosis and fracture prevention of vitamin D supplementation alone in a large, prospective, 3-year, randomized study of more than 2 500 independently-living elderly Dutch women. They received a supplement of 400 units of vitamin D_3 daily. No effect was found on fracture rate. In another, even larger, randomized, placebo-controlled and double-blind study, with 3 300 elderly women (the oldest 106 years old!) living in nursing homes in France, Chapuy et al. (1992) found that, when combining 800 units of vitamin D_3 with 1.2 g calcium supplementation the incidence of hip fractures was reduced. 20 women in the treatment group and 37 in the placebo group sustained hip fractures during the 1.5 year-study period. Moreover, Dawson-Hughes et al. (1997) in a randomized, prospective, blinded study found that daily supplementation with 0.5 g Ca and 750 IU of vitamin D to men and women living in the community and above 65 years of age reduced the number of non-vertebral fractures by more than 50%.

The only study in which one pharmacological compound was compared to another, as regards the effect on osteoporosis and fracture prevention, is by Tilyard et al. (1992) which compared the addition of active vitamin D (1.25 D_3) to 1 g of calcium in a randomized fashion over 3 years to 622 women. Half as many individuals in the group on vitamin D sustained peripheral fractures as in the group on calcium (11 vs 22 women).

The conclusions to be drawn from these, the best, studies on vitamin D and fracture prevention is that elderly individuals, especially if living in institutions, will benefit from a daily supplementation of calcium and vitamin D. The obvious difference between the Dutch study (negative result) and the French study (positive result) is that in the latter the women were older and all were living in institutions. The clinical significance of the Tilyard study is more difficult to determine. Elderly individuals who seldom go outdoors will most probably benefit from a supplementation of 0.5–1 g calcium and 400–800 units of vitamin D_3. There is no evident theoretical advantage of the vitamin D supplementation to be active vitamin D. Cholecalciferol or ergocalciferol is cheap and in the doses suggested above, also safe. Only in extreme cases with, for instance, renal insufficiency, is there a need for the use of active vitamin D with the potential side-effects related to that drug.

Estrogen

In the postmenopausal period, there is an increased rate of bone loss per unit of time. We have abundant evidence that estrogen therapy can stop this bone loss, and even reverse it. More than 20 prospective, randomized, blind studies on estrogen supplementation and bone mass have been published (for review, see Johnell 1995). These studies provide convincing evidence of a difference—an average 3% per year—between the estrogen-treated probands and the controls. However, all but one of these studies were performed in young, postmenopausal women, the only exception being a study by Lufkin et al. (1992). This was a 1-year prospective study of 75 women. This is also the only prospective, randomized study on estrogen, attempting to identify individuals with fractures sustained during the study period. However, the subjects were far too few to give any unequivocal information. These studies thus show that bone mass increases, at least for a few years, when postmenopausal women are given a supplement of estrogen—whether it is conjugated estrogens (≥ 0.625 mg per day), oral estradiol (≥ 2 mg per day) or transdermal estradiol (≥ 50 µg per day). Additional supplementation of progestogen also is always necessary in non-hysterectomized women, to prevent stimulation of the endometrium. There are no data concerning estrogen treatment of older women. To judge whether there is a long-term effect of estrogen or not, we have to rely on retrospective data or—better—prospective cohort studies on estrogen and fracture. Three large studies of this type, each including 9,000–23,000 postmenopausal women, have come to roughly the same conclu-

sion—estrogen reduces the risk of hip fracture in current users and in recent users, while users who stopped the estrogen therapy many years ago were not protected (Naessén et al. 1990, Paganini-Hill et al. 1991, Cauley et al. 1995). These three studies have in common the age-segments studied, namely, the early postmenopausal period. Considerably less than 10% of all hip fractures occur at this period in a woman's life. The effect of estrogen treatment for the prevention of fracture and from the community's point of view may thus be limited.

Bisphosphonates

Bisphosphonates are chemical products which have been well known for more than 100 years. Not until recently was it discovered that they have a potential effect on bone metabolism by blocking the recruitment and activity of osteoclasts (for review, see Fleisch 1997). Since osteoblasts are not influenced negatively, at least not to the same extent as osteoclasts, the net result is bone gain. Several different bisphosphonates are registered in different countries for the treatment of various metabolic bone diseases with osteoclast overactivity, such as hyperparathyreoidism, Paget's disease or malignant hypercalcemia. To date, two of the compounds have been investigated in prospective, randomized, double-blind trials on osteoporosis and fracture prevention. These two are etidronate and alendronate. Other compounds are being tested in large trials.

Etidronate has been investigated in two independent trials, reported in three papers. The first trial was performed in Denmark in 1990 by Storm et al. (1990). 66 women (56–65 years old) were followed for 3 years. Clearly, there was no difference in the number of women with or without fractures in the treatment group, compared to the placebo group. The number of probands included was far too small. In another study (American), however, also published in 1990, by Watts et al., 429 women not older than 75 years were included and followed for 2 years. The inclusion criterion was the presence of 1–4 vertebral fractures. The numbers treated in the active and the placebo groups were not exactly the same, but extrapolated figures reveal that 8 compared to 18 women had new vertebral fractures, thus showing a significant protective effect of etidronate. However, Harris et al. in 1993 reported the outcome after a 1-year extension of the Watts' study referred to above. After 3 years, 28 vs 34 women had new vertebral fractures—thus the significant difference between treatment and control groups had disappeared.

Alendronate has been investigated in two considerably more expensive studies, which were deemed to be sufficiently rigorous to detect possible differences. In the first of these studies, by Liebermann et al. in 1995, the inclusion criteria were that the 994 women were postmenopausal, 45–80 years old and had osteoporosis. After 3 years, 17 of the treated women had new vertebral fractures, compared to 33 of the controls (also here, the two groups were of different sizes, so the figures are extrapolated by the author). In another recently published study (Black et al. 1996), 2,027 women, 55–81 years old, with a low bone-mineral density of the femoral neck, were randomized in an intended 3-year study which, for reasons of efficacy, was stopped after 2.9 years! There was a 47% reduction in the incidence of patients who had at least one new vertebral fracture (78 women in the treatment group, compared to 145 women in the placebo group) and an astonishing 90% reduction in the incidence of patients who had 2 or more new vertebral fractures (5 compared to 47 women). Not all of these vertebral fractures were clinically significant, but there was a reduction in the incidence of symptomatic vertebral fractures (23 vs 50 women). There was also a reduction (just significant) in the incidence of patients having hip fractures (11 vs 22 women). In addition, the number of patients having wrist fractures was reduced (22 vs 42 women). In the above-cited studies on etidronate and alendronate, bone mass measurements were also performed. An increase of 2–9% in the periods studied and in different parts of the body was found.

The absorption of bisphosphonates in the gastrointestinal tract is poor—for certain compounds, less than 1% of the ingested amount. Absorption is even further diminished by concomitant ingestion of other medicines or food. Therefore, these compounds must be taken on an empty stomach and the patient must refrain from eating and drink only water for a while thereafter. The part that is absorbed goes either directly to the skeleton or is excreted unmetabolized in the urine. The fact that the bisphosphonates are not metabolized in the liver may be one of the reasons why there are so few-mainly gastrointestinal-adverse effects.

Existent and new biphosphonate compounds thus have a promising ability to prevent fractures. One drawback is that there may be some, as yet unknown, long-term, negative effects. It is therefore advisable that the compounds be used with strict indications, until a few more years have passed and our knowledge has widened. By then, we may also have found out from ongoing studies whether there is a plateau effect on bone mass after some years of treatment or whether the treatment should be continuous or in periods of one or a few years.

Other pharmaceutical treatments

There are many other pharmaceutical compounds used world-wide for the treatment of osteoporosis. Two of the best established are fluoride and calcitonin. There are randomized, double-blind studies on these compounds, where bone mass and fracture rate have been evaluated. However, none of them has been sufficiently large to have the power to reveal a positive effect. There is no doubt that fluoride treatment results in increased bone mass, but the bone produced may not be normal. Furthermore, substantial side-effects of fluoride treatment have been found in a few studies (Riggs et al. 1990, Kleerekoper et al. 1991, Pak et al. 1994). Concerning calcitonin, there is a positive effect on bone mass, but no ascertained effect on fracture reduction (Ljunghall et al. 1991, Overgaard et al. 1992).

Anabolic steroids are also sometimes used, especially in elderly individuals with both low bone mass and low muscle mass. Although there might be a positive effect on bone mass, the effect on muscle mass and thus a possible effect on balance may be more important. We have no evidence for fracture prevention with this drug. Nor do we have any evidence for fracture prevention with newer drugs such as anti-estrogens, prostaglandins, parathyroid hormones or various growth factors.

Targeting the individual-at-risk

The successful fracture prevention found in recent, large, prospective, randomized studies of new pharmaceutical compounds may change the clinical situation for orthopedic surgeons—provided we can identify the individuals at risk.

There are perhaps hundreds of more or less well established risk factors for osteoporosis and fractures proposed in the literature. Apart from age, female gender, recently sustained fracture, heredity of osteoporosis or osteoporotic fracture, early menopause, history of eating disorders, immobilization and treatment with corticoid steroids are well established risk factors. Low bone mass, as assessed by different techniques for bone mineral measurement, is a major risk factor for fractures (Cummings et al. 1995). Screening of populations for osteoporosis is probably not to be recommended. Screening individuals at risk with bone mineral measurements is, on the other hand, advisable, provided the patient has a positive attitude towards treatment.

Which patients will benefit from a bone mass measurement?

In my opinion, all individuals up to the age of about 80 years, presenting with at least two or three of the above risk factors and with a positive attitude towards pharmacological treatment, should have a bone mass measurement performed. With modern technology, this is a cheap and fast procedure, providing good, predictive information on the risk of forthcoming fractures. Today the required technical equipment is available at almost every hospital and the installation rate of new machines is speeding up. I believe that measurement of the very elderly is not feasible since, as a direct consequence of the definition of osteoporosis, almost 100% of them are osteoporotic and the existence of risk factors other than low bone mass may be more important for the decision whether or not to give pharmacological treatment. The above-stated opinion implies that almost all postmenopausal women with fractures sustained after low-energy trauma are at risk for further fractures and should have a bone mass measurement done, if they are not too old. The number of individuals referred for bone mass measurement would thus by far exceed the facilities available today and therefore, as yet and for practical reasons, it will be mostly the women who themselves bring up a discussion of these matters with their physician, and women presenting with several risk factors for osteporosis, who will today be offered this examination. On the other hand, it is not always necessary to do a bone mass measurement before pharmacological treatment is initiated. As mentioned earlier, this may not be necessary for the very old. Women taking estrogens for reasons other than fear of osteoporosis will not benefit from a bone mass measurement, as this will not change their attitude towards estrogen treatment.

Who should treat and how to treat?

Let it be understood that the treatment of osteoporosis has already today become a routine procedure for the general practitioner. The orthopedic surgeon, unwilling to handle this, can therefore always refer the patient before or after a bone mass measurement has been performed.

There have been a number of consensus conferences and reports from different national pharmaceutical agencies as to which treatment for osteoporosis that is to be preferred and at what age. The recommendations from these reports vary very little. There is consensus that young, postmenopausal women, up to an

age around 70 years would benefit from estrogen. So long as this treatment does not exceed 10 years, there seems to be no increased risk of cancer of the breast. Nevertheless, the treatment should be given by a gynecologist or a general practitioner, with regular check-ups including mammography.

In older women, a sufficient intake of calcium and vitamin D should be assured and all elderly women treated because of recent osteoporotic fractures and living in institutions should, according to the author's opinion, have a supplement of at least 0.5 g of calcium and 400 international units of vitamin D daily. Those who drink or eat very little dairy products and never go out will probably benefit from even 1 g of calcium and 800 international units of vitamin D daily. With the existing shortage of equipment for bone mass measurement, such treatment can be initiated without a previous bone mass assessment in this group of elderly women.

Women not willing to take estrogens or women with gynecological disease contraindicating such treatment will benefit from bisphosphonate treatment. This is probably also true of men with osteoporosis, although data for men are still lacking. Which specific compound should be used is a matter of debate, but alendronate is by far the best documented product with osteoporosis as indication. We do not know yet for how long treatment with bisphosphonates should be continued but, since bone mass increases by almost 10% in 3 years, most of these individuals will no longer be osteoporotic after this treatment and after this period. Therefore, it seems possible that future therapeutic regimens with this type of compound will be for instance, 3 years on, 1–2 years off and so on.

This article was written because it is my firm opinion that we orthopedic surgeons also must have a certain level of knowledge of risk factors and pharmacological treatment of osteoporosis. Since patients with osteoporosis normally have their first medical consultation for this condition with an orthopedic surgeon, it is our responsibility to arrange a bone mass measurement to be done and/or to get professional advice on whether or not to prescribe active drugs.

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