Round-Table Discussion on Prevention of Osteoporosis

Dr. Hodkinson: I should like to ask Dr. Bonjour whether, in his second study where he was comparing protein versus no protein supplements, the supplements were of equal energy value.

Dr. Bonjour: There was a difference of 10% in the total energy consumed between the two groups.

Dr. Hodkinson: In your first study, your supplement, which was highly successful, provided around 15% to 20% additional energy, so if there was an energy imbalance of 10% in your second study, it could be significant.

Dr. Rush: I am concerned about the subjectivity of the end-points. Although the patients obviously could not be blinded to their treatment, some observers could have been. Did you use any other end-points apart from length of hospital stay, which seems to me to be very insecure since it could be affected by knowledge of treatment on the part of both the patients and the care-givers?

Dr. Bonjour: What suggestions do you have, accepting that double blinding is impossible?

Dr. Rush: There are various intermediate strategies. For example, the study could be single blinded to a set of observers who were asked to do an objective assessment of nutritional status or functional status, or whatever indices you accept as being relevant to the effect of the protein supplement. The length of hospital stay is not an end-point I am comfortable with, unsupported by other end-points.

Dr. Bonjour: Your point is well taken. We are not saying that what we have presented here is the end of the story. Other studies need to be done to confirm what we have found, using different outcome variables as you propose. Another thing we have not touched on is the mechanism; I think we need to measure possible mediators such as insulin-like growth factor (IGF) in these patients.

Dr. Guesry: It is said that peak bone mass is acquired between the 16th and 21st years of life. This rather implies that after 20 years of age nothing much can be done to improve the situation and delay the occurrence of hip fracture. What is your view on this? Should teenagers be advised to take more vitamin D and bone minerals? They don’t worry much about what is likely to happen 50 years later!

Dr. Bonjour: I’m not sure that we really know at what time of life we can obtain most benefit from giving additional nutrients such as calcium. We need longitudinal data showing that enrichment of the diet with calcium and perhaps energy during the rapid phase of bone mass accumulation is effective in increasing bone mass. Studies in monozygotic twins have shown an effect of calcium supplementation but it is rather small and only certain areas of the skeleton appear to be significantly affected. Between the ages of 20 and 45, the period when bone mass seems to be more or less stable no study has so far demonstrated a major change in bone mass by supplementation or by exercise. As far as the elderly are concerned, I should like to have Dr. Meunier’s comments because he has interesting data on supplementing elderly people with calcium and vitamin D.
**Dr. Meunier:** In parallel with the exponential increase in incidence of femoral fractures after the age of 80, there is continuing bone loss. We have shown recently in a cross-sectional and prospective study that the bone loss at the upper end of the femur is of the order of 2% to 3% per year until death and is associated with very high parathyroid hormone (PTH) values. When ambulatory elderly people with high levels of PTH are treated with supplements of calcium and vitamin D₂ or D₃, the PTH values fall by about 45% in 18 months and there is a cessation of bone loss from the upper femur. So it is never too late—we can still protect bone after the age of 80 with vitamin D and calcium supplements.

**Dr. Berry:** Since bone density depends on both calcium and bone matrix, which is protein collagen, is there any evidence that a low protein intake, in the presence of an adequate calcium intake, can lead to osteoporosis?

**Dr. Bonjour:** From what I know about the relationship between protein and osteoporosis in several human studies, I think it is very difficult to isolate protein from other nutrients in terms of individual responsibility for low bone mass.

**Dr. Lindsay:** I should like to comment on the hip fracture issue. Bone mass is a risk factor for hip fracture but it does not diagnose hip fracture, and the concept of bone mass separating fracture from nonfracture cases is of no great importance. When examining data in which people with hip fractures have been compared with age-matched controls, it is apparent that all old people have a low bone mass, so all are at risk of fracture. In cross-sectional data you are comparing those who have had a chance occurrence with those who are waiting for that chance occurrence to happen. Everyone who lives long enough, be they male or female, black or white, will become osteoporotic and will be at risk of fracture. At the same time, because they are getting older they will have an increased risk of falling and fallers are the ones most likely to get fractures.

**Dr. Steen:** I have a question for all the participants about the relative importance of different risk factors for osteoporosis. Judging from our longitudinal studies, we are of the firm opinion that there are two main risk factors and these are physical inactivity and smoking. Compared to these, the other known risks (calcium, estrogen, and so on) are relatively unimportant. Smoking has not been focused on as much as it should have been in this conference. When, in our analysis, we keep physical activity, alcohol intake, and body weight constant, we have a 30% difference between smokers and non-smokers in bone mineral content at age 70 years. Smoking is an important risk factor for osteoporosis.

**Dr. Lindsay:** I don’t think anyone would disagree that smoking is a risk factor. However, if we look at this from the point of view of behavior modification, it is evident that it is very difficult to get people to give up smoking, even when they are threatened with much more serious risks than osteoporosis.

One of the concerns I have about bone mass as an outcome variable for interventions such as physical activity, nutrition, and so on, is that the methodology of bone mass measurement is very dependent on body composition. Thus, the changes one sees, if not adequately corrected for differences in body composition, will result in apparent differences that are perhaps much greater than the real differences.

**Dr. Guesry:** At a recent symposium in Lausanne on the prevention of osteoporosis, a group from Zurich reported on risk factors. Cigarette smoking appeared to play only a small role. Do you have any theory on the possible mode of action?

**Dr. Steen:** No, I don’t. It is of course possible that there may be confounding factors and that smokers have other characteristics that put them at risk for osteoporosis. However, when we try to hold the other known factors constant in the analysis, there are still very large differences in bone mineral content between smokers and non-smokers at age 70 years.
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Dr. Edwardson: I wonder what proportion of women in the age range of 70 to 75 years are smokers. I thought it was relatively small.

Dr. Steen: Although the proportion of smokers among women is definitely lower than among men, it is showing a dangerously increasing trend, in my country at least. Young women smoke very much more now than they did a couple of decades ago.

Dr. Lindsay: For the most part, of course, cigarette smokers don't live long enough to get hip fractures. However, it is worth recalling that smoking is associated with changes in estrogen metabolism resulting in a reduction in endogenous estrogen supply, perhaps making the need for exogenous estrogen greater.

Dr. Edwardson: Repeated studies in Newcastle and elsewhere in the United Kingdom have shown that 25% of hip fracture patients are severely demented and a further 50% show significant cognitive impairment. This is not simply a post-traumatic confusional state because repeat studies 6 months later show virtually the same cognitive test scores. In case there might be some underlying relationship between negative calcium balance and cognitive impairment, we have looked at bone mass in severely demented hip fracture patients in comparison with hip fracture patients of the same age with normal cerebral function and there is no difference at all. This suggests that the crucial risk factor is the predisposition toward falling related to cerebral impairment.

Dr. Lindsay: I hope I didn't give the impression that the answer to hip fracture is necessarily a pharmacologic intervention targeting the skeleton. That is one factor in the hip fracture equation. There is no doubt that falling is also an important factor, particularly in the nursing home population. However, falling is not a factor in vertebral crush fracture risk, and this type of fracture occurs in people going about normal daily activities. I think that the prevention of bone loss is likely to be important in reducing the incidence of all fractures.

Dr. Rush: It seems fairly clear that estrogen therapy is now being used widely and for prolonged periods, but what is known of the ultimate cost-effectiveness of estrogen in relation to osteoporosis and also in relation to other diseases such as cardiovascular diseases and cancer of the breast? What is the balance of risks associated with long-term estrogen therapy?

Dr. Lindsay: The epidemiological data are consistent in showing that the use of estrogens by themselves is associated with a reduction in the relative risk of cardiovascular disease in postmenopausal women. This may in part be related to changes in lipoprotein metabolism. The reduction in risk of death from cardiovascular disease, which is the most common cause of death in postmenopausal women in the United States, is of the order of 50% with estrogen therapy. However, it must also be said that the use of estrogen alone increases the relative risk of developing endometrial cancer by two- to eightfold. Survival from endometrial cancer is almost 100%, and the survival in estrogen-treated women is even greater than in women who have not received estrogens, for reasons I don't completely understand.

The issue of breast cancer is much more complicated and potentially problematic. My conclusions from the currently available data are that estrogens increase the risk of breast cancer by between 10% and 30% when treatment has been given for prolonged periods, that is, 10 years or more. There are data to show that the increased risk ceases to be present when estrogens are discontinued, which leaves me rather concerned about the mechanism. The implications of these data are that the risk of developing breast cancer in the average postmenopausal woman of 50, which is normally about 1:9, will increase to 1:8. Since breast cancer is so common, this represents a fairly important increase in the potential total numbers of malignancies. However, I am unaware of any studies that have shown higher mortality from breast cancer in estrogen-treated postmenopausal women, and in fact several show decreased mortality. The reason that women discontinue estrogen replacement therapy in
the United States has little to do with cancer. It is because cyclical menstrual bleeding is socially unacceptable after the age of 50. Until we find a mechanism for prescribing estrogen, with or without progestin, that does not produce endometrial bleeding, this will continue to be a problem.

Dr. Rush: I think the apparent disparity between incidence and survival in the breast cancer data is not something I should be at all confident in. It has been shown clearly that women who receive estrogens are from a different social class background and are exposed to a different level of medical care.

Dr. Lindsay: There is no doubt that part of the survival difference is related to detection by physicians; that is, women on estrogen are more likely to have a malignancy diagnosed at an early stage because it is looked for.

Dr. Glick: I am not clear about whether there is information on the net effect of exercise on bone strength.

Dr. Meredith: The final message is that exercise, if it is frequent enough and vigorous enough, will affect bone density at any age, just as immobilization will affect it in the other direction at any age. In young military conscripts exposed to heavy physical training schedules, the increase in bone density is of the order of 11% over a period of weeks, although a number of recruits suffer fractures. It appears that we need to balance the amount of exercise taken such that it is sufficient to increase bone density without causing fractures.

Dr. Glick: Is the regular exercise involved in normal day-to-day activities meaningful in maintaining bone structure?

Dr. Meredith: Your bone mass is appropriate for a certain level of exercise. If you decrease your level of exercise bone mass will also decrease, but no further than a certain set point. If you abruptly increase or decrease your habitual exercise the bone mass set point will change.

Dr. Chen: What about medications as risk factors for osteoporosis? I am concerned particularly about diuretics, which may deplete calcium.

Dr. Lindsay: Medications are important causes of secondary osteoporosis, not only diuretics but also overtreatment with thyroid hormone (even when given as replacement therapy), and of course glucocorticoids. One problem related to calcium deficiency is that we don’t really know how to define it since there is no test for it.

Dr. Guesry: Don’t you think that secondary (presumably) hyperparathyroidism is a good indicator of calcium deficiency?

Dr. Lindsay: I don’t think it is sensitive enough. Although there is an adaptive mechanism to increase calcium absorption in the face of calcium deficiency, involving increased PTH and stimulation of 1.25(OH)2D, this varies considerably from person to person, and PTH may not go outside the normal range in some people with calcium deficiency.

Dr. Chen: The RDA for calcium was revised in 1989. According to the revised values, the RDA for a woman of 50 is 800 mg. Is this an adequate amount for a woman in this age group?

Dr. Bonjour: I think 800 mg is probably enough but there are many studies showing that in the 5 years after menopause even if you increase the calcium intake to 1,200 or 1,300 mg per day you cannot stop the bone loss, so maybe we should be giving even more.

Dr. Guesry: Is there any information about the effect of fluoridation of water supplies on bone mineralization?

Dr. Meunier: A study was reported in the Lancet by Simonen and Laitinen (1) in which they investigated the effect of water supplemented to a level of 1 mg fluoride ion per liter. There was a lower incidence of femoral fracture in the group receiving this small dose.
Dr. Guesry: This is quite encouraging because this level of fluoridation is free of side effects.

Dr. Meunier: Some mineral waters available in France are rich in fluoride. We have investigated 23 heavy drinkers of one particular variety of mineral water containing 8.5 mg fluoride ion per liter, which is a lot. We found a significant increase in lumbar bone mineral density in these people without any symptoms of fluorosis.

REFERENCE