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Leading Article

Osteoporosis – an opportunity to prevent being missed

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Osteoporosis is defined as a decreased amount of bone but is recognized clinically as increased risk of fracture, and the sufferer often not identified until after that event has occurred. Many who sustain a fracture are even then not recognized as suffering from underlying osteoporosis. Although the event of fracture depends on falling and poor protective responses, the final common pathway for this event is increased fragility of bone due to loss of bone mass and microarchitectural deterioration. It is a major cause of mortality and morbidity. There are in the order of 130,000 vertebral fractures, 40,000 distal forearm fractures and 50,000 proximal femoral fractures a year in Great Britain most of which are due in part to osteoporosis.[1] The lifetime risk of Caucasian women of sustaining a distal forearm fracture is 15% and of proximal femur fracture is 15%.[2] This compares to 8% for breast cancer and 9% for cerebrovascular accidents. Most proximal femur fractures occur in the elderly, and the annual incidence increases from 1–2 per 1,000 65 year old women to 25 per 1,000 85 year old women and from 0.5–1 per 1,000 65 year old men to 10 per 1,000 85 year old men.[3] Twenty-five to 30 per cent of these will die within 6 months, more than half the survivors will suffer increased disability, and 20% will lose independence.[3,4] The care of these hip fractures in hospital and the community is estimated to cost £500 million per annum.[5] A 15% increase in proximal femoral fractures can be expected over the next decade because of the increase in the ageing population[5] but, in addition, the incidence rate has been shown to be increasing[6] and this fracture could increase by 50% in a decade. It is recognized by government that this is the next disease to be prevented in women's healthcare following the screening campaigns for breast and cervical cancer, but is it preventable? Can the incidence of fractures be reduced? Is there a population wide strategy that could be adopted?

Fracture is a consequence of loss of bone mass with microarchitectural deterioration, loss of protective responses and falling. Although the latter two are the discriminators as to who does or does not fracture in the very elderly,[7] as all at that age have a low bone mass, osteoporosis *per se* is an important risk factor for fracture below 75 years. Prevention of fracture involves preventing all three.

Falls are common in the elderly; 1 in 4 over 65 years will fall in the subsequent year and 5% will result in a fracture.[8] Half occur in the home and half are due to environmental factors, most commonly those falls occurring away from home. There are specific preventable causes, such as sedatives, iatrogenic postural hypotension or arrhythmia, but more commonly there is a combination of factors resulting in decline of neurological and musculoskeletal function.[8,9] Prevention is dependent on maintaining the general health and functional abilities of an ageing population. Such an approach is safe and could be applied population wide but we do not know if this would have a major effect on fracture incidence. Those who have already fallen are at most risk of further falls[8] and alternatively this group could be targetted for medical and social assessment and input. The occurrence and physical impact of a fall relates to protective response and reflex time increases with ageing. Maintaining physical activity and fitness may reduce risk of falling[10] and of subsequent fracture by maintaining these protective responses, but the effectiveness of this needs to be established and it will increase potential for falls.[11] However, although the risk of falling doubles, the risk of fracture increases 20-fold from 65 to 85 years.[3] This exponential increase is typical of a condition that is the clinical manifestation of the combination of many factors, some of which are increasing with age. Falling is one of these, but the probability of a fall resulting in fracture is modulated by other factors that have an increasing effect with age, such as osteoporosis.

Strength is related to bone mass and the prevalence of fractures increases with lower masses at all ages.[12] Bone mass attained at midlife predicts the risk of future fracture[13,14] but there are other contributors to fracture risk. As bone is lost there is an increase in microfractures and loss of trabecular connectedness.[15] The thinning and discontinuity of

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trabeculae results in increased fragility. It is questionable whether this is reversible and the maintenance of bone mass is the mainstay of prevention. How can bone mass be maximized and loss prevented?

Dent described osteoporosis as a disorder of ageing with its origin in paediatrics.[16] The determinants of peak bone mass are not fully established. It appears that genetic factors determine potential peak bone mass and sensitivity to environmental factors such as hormonal exposure, skeletal loading and diet which influence the attainment of that peak.[17] Reduction of exposure to female sex hormones during growth and development, such as Turner's syndrome or other forms of gonadal dysgenesis, is associated with reduced bone mass.[18] Short periods of low oestrogen levels, such as hyperprolactinaemia, are also associated with decreased bone mass.[19] The effect of dietary calcium is debated[20–22] but lifetime intake may influence peak attained and subsequent risk of fracture.[23]

Skeletal loading is a potent stimulus to bone remodelling and strength[24,25] but it is not clear the magnitude required, regional specificity, time of life most effective and potential for difference. Both diet and exercise could be threshold phenomena with the most important differences achieved by increasing from slight deficiency to adequacy. Immobility results in bone loss[26] and weight bearing exercise is effective during growth and development in increasing bone mass[27] and in later life in reducing bone loss.[28,29] Exercise exerts a local effect on the skeleton and maximum stress is associated with the largest increases.[27] Its role in later life may be just restoring a normal amount of loading to the skeleton that has been lost with our relatively new sedentary lifestyles. The effect of oestrogen cannot be compensated for by exercise. Amenorrhoeic athletes demonstrate that hormones are more important than exercise.[20,27,31]

Bone loss begins at midlife and the association between loss of bone mass and the menopause was first suggested by Fuller Albright in 1940[32] and is best demonstrated in women following oophorectomy.[33] Hormone replacement therapy (HRT) will prevent this bone loss at trabecular and cortical sites throughout the skeleton[33–36] and most importantly has been shown to reduce risk of fracture.[37,38] Prospective studies of continuous oestrogen in oophorectomized women have shown maintained reduction of bone loss at 10 years of treatment[34] and that starting treatment after 6 years prevented further loss but did not restore mass. Initiation of HRT close to the menopause is therefore necessary to maintain peak bone mass.[34,36] With discontinuing HRT, bone mass is lost but the gain during the years of treatment is maintained,[36] although duration of effect after cessation is unresolved. Retrospective case-control and prospective cohort studies have shown a major reduction of risk of fractures in the order of 35–50%[37,38] with oestrogen replacement for 5 years. There will also be a reduction in fatality associated with femoral fractures. HRT may be given orally, percutaneously or by implant. Prevention of bone loss is dose-dependent with a plasma oestradiol concentration of 150–200 pmol/l following percutaneous administration, or a minimum daily dose of 15 μg of ethinyloestradiol, 2 mg of oestradiol or 0.625 mg conjugated equine oestrogens necessary.

To balance this benefit there remains some concern about increased risk of breast cancer with long term HRT. There have been numerous studies and the effect of HRT on the breast remains controversial. There is no significant increase in risk with 5 years use.[39] There is an increased risk associated with use of continuous oestrogens for more than 10 years,[39] with relative risks of 1.3–2.0 from various case control studies.[39] A large study has shown an increased risk of 30% with 10 years' continuous oestrogen therapy.[40] Risk associated with using the present regimes of continuous oestrogen and intermittent progestrogen is unresolved as is the case fatality of HRT-associated cancer. Continuous oestrogen, but not combined therapy, is associated with an increased risk of uterine cancer[41] and should only be used in hysterectomized women. It is, however, associated with a 50% reduced risk of ischaemic heart disease[42] making a strong case for all hysterectomized women to receive continuous oestrogens.

Despite these proven benefits and few side effects, perimenopausal use of HRT by women consulting their general practitioners about the climacteric was only 3.8%[43] in one survey, and in another only 18% of post-menopausal women had ever taken HRT for a median duration of 11 months; only 25% of hysterectomized and 30% of oophorectomized women had received HRT for a median of 24 months.[44] Why? The only absolute contraindications are carcinoma of the breast and uterus, pregnancy and undiagnosed vaginal bleeding. Other factors such as previous deep venous thrombosis, hyperlipidaemia and hypertension are only relative contraindications although frequently stated as reasons for not giving patients requested HRT. Any specialist can recommend HRT as its initiation and supervision can, in most circumstances, be by general practitioners. Pelvic, breast examination with mammography, and a general examination should be performed before initiation but no endometrial biopsies are necessary unless there is irregular bleeding.

Bone loss can also be reduced by exercise,[28,29] calcium supplementation,[30] and agents such as calcitonin,[45] bisphonates,[46,47] fluoride,[48,49] anabolic steroids[50] and parathyroid hormone.[51] At the

menopause they are relatively ineffective compared to hormone replacement therapy and the effect on future fracture incidence is unknown. Exercise and calcium are, however, safe, well tolerated and acceptable. The long term data on efficacy and safety of the other treatments is awaited before they can be considered as a routine alternative for primary prevention, but they have been demonstrated more clearly to be effective in established cases of osteoporosis.[46-48]

What strategy should be used to reduce the incidence of fractures in the community as a whole? For any strategy to be effective it must be applicable to the at risk population. One could argue that a 15% lifetime risk of proximal femur fracture and a 20% incidence of vertebral fractures over 70 years[2] justifies applying any strategy to the whole female population. It would have to be widely acceptable and safe. Effectiveness is less important if the strategy reaches the whole population and reduction in fracture incidence would be better than compared to a very effective therapy that is only acceptable or applicable to a few. There is no doubt that HRT taken for 5 years will dramatically reduce risk for the individual[37,38] but it will only reduce the incidence of fracture in the population if a large proportion of postmenopausal women take it. That is not so at this present time.[43,44] Can the proportion of the population reached be increased or should we consider more acceptable but less effective approaches? Increasing the acceptability of HRT requires a greater awareness of the problem and of the effectiveness and safety of HRT – education of the medical and lay public.

Although risk of osteoporosis is high, it is not universal and an alternative 'high risk' strategy of screening for and only treating, those most at risk may be more acceptable. This would have an impact on fracture incidence if sufficient of those at risk were reached and adequately treated. Can we identify such a high risk group? Many risk factors have been identified, such as Caucasian races, early menopause, nulliparity, low body weight, corticosteroid therapy and excessive alcohol intake, but either the relative risk or their prevalence is too low for there to be a major impact if they were removed.[52,53] Bone mineral assessment is becoming increasingly available and proposed as a useful screening tool.[54] Low bone mass at midlife is associated with an increased risk of future fracture.[13,14]

The limitation of this approach is the applicability of screening and treatment. Only 40% of the population usually avail themselves of a screening programme such as for breast cancer, and one can estimate from present experience that less than 50% of these menopausal women commence HRT with the intention to prevent osteoporosis, and only 25% of these are likely to be on treatment at 1 year. Although screening and demonstration of increased risk may increase uptake and long term compliance, many of these women are probably those who are sufficiently concerned to have taken HRT anyway. It may influence these women to take long term treatment but it is uncertain whether this strategy will dramatically increase applicability of this therapy in the community and its impact will therefore be limited despite the effectiveness of treatment. There remain many myths held by doctors and the public about the effectiveness and safety of HRT if given for the necessary 5 years to reduce fracture risk, which prevent its use and need to be corrected by education. There are genuine reasons for non-compliance such as the concept that taking HRT is unnatural and the recurrence of menstruation is not always acceptable. Newer hormone preparations may overcome the latter obstacle. HRT may, however, never become the mainstay of fracture prevention because of this limited applicability.

What of the alternatives? Calcitonin and etidronate reduce bone loss[45-47] and recent studies of etidronate show prevention of fractures in established osteoporosis[46,47] but these agents are unlikely to be used universally in primary prevention until further data is available showing long term efficacy and safety. More applicable simpler alternatives need to be further assessed, such as diet and exercise. Despite the uncertainty of how effective calcium supplementation is,[20-22] even a small effect on bone loss and fracture incidence would be significant in fracture prevention. A drug that is only 1% more effective than placebo in reducing the incidence of fractures would prevent more than 1,000 fractures a year in Britain.[21] High fluoride intake in drinking water is associated with higher bone mass[55] and reduced incidence of proximal femur fractures.[56] Exercise may have sufficient applicability to outweigh its limited effectiveness on bone mass and protective responses. These general measures may eventually succeed as a population strategy in preventing fractures, but for the individual there is no doubt that HRT is effective at preventing osteoporosis and fracture, safe and deserves wider use.

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