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THE ORIGINS AND PREVENTION OF OSTEOPOROSIS IN WOMEN

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Osteoporosis is not restricted to females nor to the aged, but it is upon the elderly white female that the principal burden of the disease descends. A brief review must necessarily be eclectic and I will therefore concentrate on the problems of aetiology and prevention as they affect female patients in the UK.

Osteoporosis is a condition which is specifically managed by a few specialist physicians but which is encountered by virtually all general physicians, and certainly by all general practitioners. The increasing longevity of the population alone will ensure that, unless the condition exhibits an unforeseen decline in prevalence, it will present an ever-greater challenge to the public health - and to the public purse.

The condition is certainly prevalent. The number of osteoporosis-related fractures in the United Kingdom is about 150,000 per annum.[1] It is estimated that, for example, there will be some 50,000 femoral neck fractures in the UK this year, of which about 25% will result in the death of the patient within six months, and approximately 50% of the survivors being unable to return to independence in their own homes.

Osteoporosis is defined by the World Health Organization as:

> A disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. (WHO, 1994.)

Quantitatively, it is deemed to be present when the bone mineral density (BMD) at a skeletal site falls to 2.5 Standard Deviations (SD) below normal for that site in a healthy young adult. Similarly, the intermediate condition of osteopenia, low bone mass, is indicated by a BMD ranging from 1-2.5 SD below the young adult mean.[2]

BONE REMODELLING

In osteoporosis there is not enough bone tissue per unit volume to enable the trabeculae, which comprise the internal architecture, to discharge their engineering function: shock absorption (Figure 1). To understand how this occurs, we must understand that bone is regularly removed and replaced (turned over) in the physiological processes of remodelling and renewal. Bone turnover occurs in an orderly and unvarying sequence of bone removal; pause; bone formation. This sequence occurs at microscopic sites throughout the skeleton known as Bone Remodelling Units (BRU) and a healthy adult can expect to have around 500,000 active BRU at any one time. The process begins with a group of multinucleated osteoclasts arriving at a bone surface in response to an as yet unknown activating signal. Over a period of about six weeks, these osteoclasts excavate a cavity in the bone surface (Figure 2). They then disperse and the cavity is invaded by osteoblasts which proceed to lay down osteoid which then mineralises to form new bone, the surface of which is made contiguous with the surrounding older bone, thus concluding the process.[3]

The full timescale for the remodelling cycle of a BRU is 4-5 months. Thus it can be

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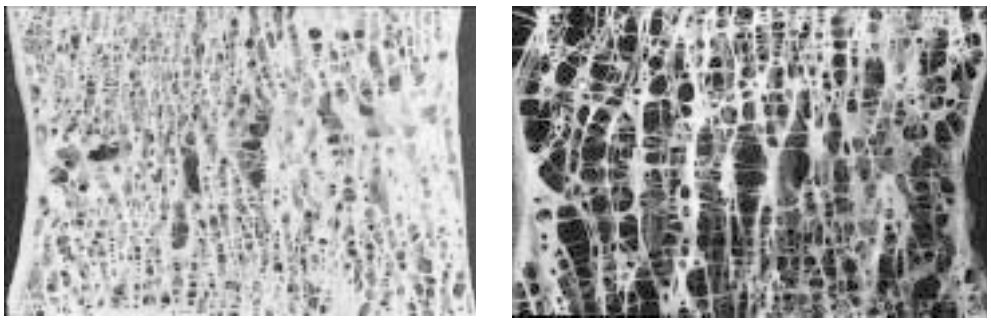

FIGURE 1
Sagittal sections of vertebral bone showing, on left normal trabecular architecture, and on right osteoporosis showing reduction in trabecular number, thickness and connectivity.

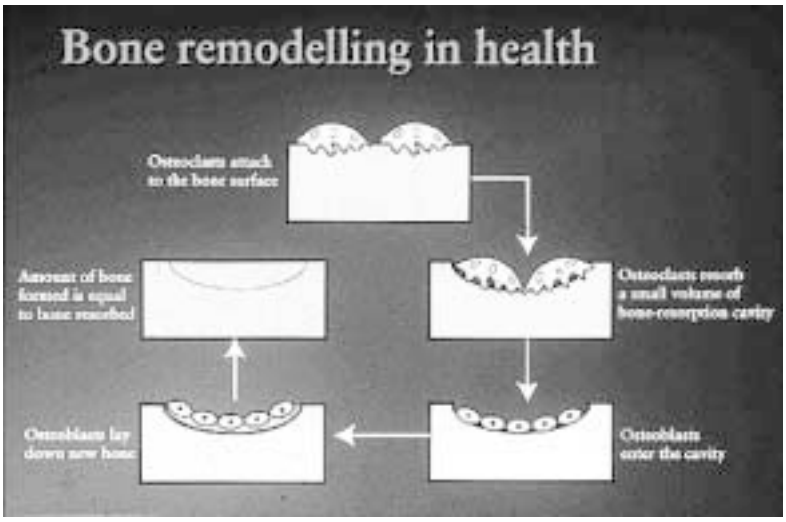

FIGURE 2
The bone remodelling cycle of osteoclast bone resorption followed by coupled bone formation.

clearly seen that the process of bone resorption must be precisely coupled with the subsequent bone formation so that bone mass ispreserved. If, for example, the rate of bone turnover is speeded up, as happens in conditions of oestrogen deficiency, a disparity emerges between formation and resorption in favour of the latter, which results in progressive bone loss.

The central variables which determine an individual's propensity to osteoporosis are:

- peak bone mass - acquired in childhood, adolescence and early adulthood,
- the rate of bone loss after menopause,
- age.

PEAK BONE MASS

Peak bone mass is a key variable in the bone economy and is largely determined

genetically, with small environmental contributions. Peak bone mass is higher in blacks than in whites, for reasons as yet poorly understood, and is higher in males than females. Clearly it is also important to exploit those environmental factors which may promote bone gain. It has been shown both in the US and in the UK that calcium supplementation of the diet of teenage girls will result in a significantly increased rate of bone gain over that observed in untreated controls.[4] Similarly, physical exercise has been shown repeatedly to confer advantages in terms of bone gain in children. Therefore, the recommended calcium intake for adolescent girls of 1.5 g per day and weight-bearing physical activities should be strongly encouraged. Conversely, the antipathy of sectors of the teaching profession to physical education and games together with the popularity of high phosphate soft drinks among the young, may adversely affect the achievement of peak bone mass.

The key areas of the skeleton which are at risk of osteoporosis are those where trabecular or cancellous bone is found in abundance. These are the spine, proximal femur and distal radius - the sites of commonly-occurring fractures in later life. Trabecular bone, comprising some 20% of the skeleton has, due to its very architecture, a relatively high surface-to-volume ratio compared to compact bone which comprises the remaining 80% of the total bone mass. Trabecular bone, with its higher turnover rate of approximately 25% per year, is thus at risk in any situation in which bone resorption outstrips bone formation; compact bone with a low turnover rate of 5% per annum is less at risk.

PROBLEMS IN ADULTHOOD

Following the achievement of peak bone mass in the mid-third decade, the bone mineral density of the key sites remains essentially stable until menopause. A slight loss at both hip and spine has been reported in some studies, but the values are small and the clinical implications negligible. In health, the next major problem that the skeleton faces is the order of magnitude fall in circulating oestradiol which accompanies climacteric ovarian failure. However, certain medical and surgical conditions may, for a variety of reasons, cause accelerated bone loss and are worthy of remark.

The investigation of secondary amenorrhoea should include measurement of the gonadotrophins, FSH and LH, and oestradiol. If oestradiol concentration is found to be in the postmenopausal range (<150 pmol/L in most laboratories) then the management should include oestrogen replacement by either hormone replacement therapy (HRT) or the combined oral contraceptive pill as appropriate. Bone loss following secondary amenorrhoea due to hyperprolactinaemia, for example, may be arrestable but not fully reversible. Hence, early diagnosis and treatment are essential.

The skeleton should be remembered in conditions such as thyrotoxicosis, malabsorption syndromes, and any condition where bone turnover is high or where gut absorption or renal retention of calcium may be impaired. Similarly, the use of corticosteroids at or above a dose of 7.5 mg of prednisolone daily, should alert the practitioner to the need for vigilance over skeletal health.[5]

The only common surgical procedure which may influence bone mass is hysterectomy, which is undergone by 20% of British women by age 50; this may be followed by a premature menopause which will be physically occult due to the post-operative amenorrhoea. Even if both ovaries have been conserved, oestrogen output may fail and plasma oestradiol and gonadotrophin estimation may indicate that replacement is required. Hence, practitioners should be advised that all patients undergoing hysterectomy should be counselled to report the onset of such oestrogen

deficiency symptoms as vasomotor upset - flushing and sweating - vaginal dryness, short-term memory loss and mood swings. The finding of low plasma oestradiol together with high gonadotrophin concentrations would then constitute an indication for replacement oestrogen.

DETECTION OF OSTEOPOROSIS

A major problem in diagnosis is the failure of clinical history to reflect current bone status. Certain risk factors are, in population terms, useful in suggesting those at risk of osteoporosis. These include: female sex, Caucasian race, early menopause, lack of physical activity and low dietary calcium intakes. Unfortunately, these population-based risk factors do not translate into a precise means of assessment in an individual patient. It is an inescapable fact that to assess bone strength the bone itself has to be visualised and its density measured. The availability of densitometry in the UK at present can be best described as patchy, although there is a general trend towards the acquisition of densitometric capability by general hospitals (Figure 3). There are several methods of bone denisty measure currently available but the present 'gold standard' is dual energy X-ray absorptiometry (DEXA).

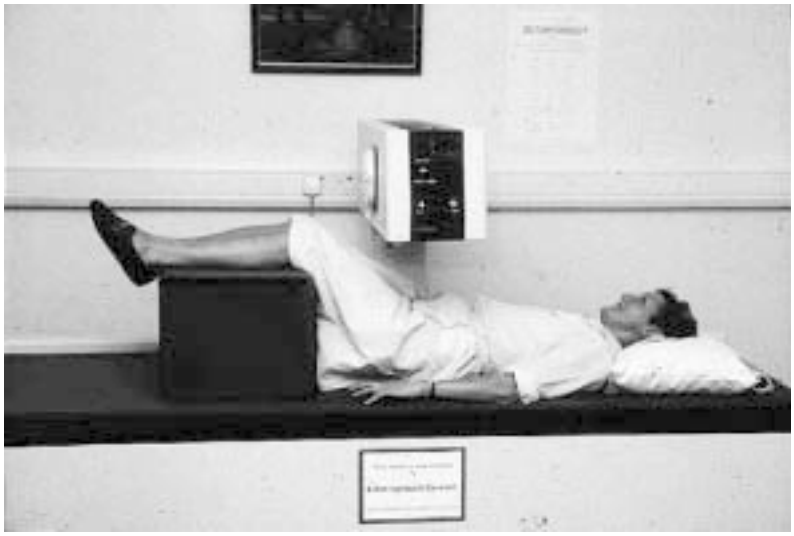

FIGURE 3
The DEXA Scanner. The patient is clothed and receives a radiation dosage of 2 pSv. Scan time for hip and spine examination is c. 20 minutes DWP-2263.

The agreed indications for the use of DEXA vary with locality. Those agreed between the author's group and the local Health Authority (East Riding Health Authority) are as follows:

1. Any oestrogen-deficient woman who would want to be treated or would want to continue treatment if found to be osteoporotic.
2. Patients suspected to be osteoporotic on the basis of radiological and clinical findings.
3. Patients who have a medical condition predisposing to osteoporosis, if effective treatment is available, including metabolic bone disease, liver disease, anorexia nervosa, malabsorption syndromes and other rarer causes of osteoporosis.
4. Patients prior to starting management with oral corticosteroids of a prolonged

duration of six months or more.
5. Patients receiving corticosteroids at a dose of >5 mg prednisolone or equivalent.
6. To monitor response to treatment in patients with established osteopenia or osteoporosis.
7. Women who experience primary or secondary amenorrhoea (including hysterectomy) below the age of 45 years.
8. Patients with a positive family history of osteoporosis in at least one first-degree relative.

Currently, until all physicians have access to a densitometric service it will not be possible to supply adequate care in the prevention and treatment of osteoporosis. However, the use of ultrasound may prove to be of value. Research into the practicality of using a low-cost portable ultrasound heel scanner continues and may yet provide a system which can be located within a health centre or participating group of centres and operated by a trained practice nurse. Such a system, if sufficiently accurate and precise, could be used to reassure the normal population and more importantly to identify those requiring further investigation by a hospital-based DEXA system.

AGENTS TO PREVENT BONE LOSS

There is general agreement that the prime agent to prevent bone loss in postmenopausal women is oestrogen. The minima for regimes of estrogen which will arrest bone loss are shown below:

Agent	Route	Daily Dose
Ostradiol	Oral	2mg
CEE	Oral	0.625mg
Oestradiol	Transdermal	50 mcg
Oestradiol	Subcutaneous	50 mg (6-monthly)

Regimens of HRT are unacceptable to many women, however, due principally to the return of cyclic bleeding and to the small but now quantified risk of breast cancer associated with oestrogen use. The breast cancer risk was recently described by a large re-analysis of published work on the issue which allowed a most useful quantification of the absolute risk involved.[6] In summary, among 1,000 untreated women aged 50, 45 cases of breast cancer will develop in the next 20 years. If the 1,000 women were given five years HRT, the number of breast cancers would rise to 47 and, after 10 years of HRT, to 51. Although the absolute increase in risk is relatively small it is still sufficient to discourage many women from taking HRT at all. The advent of the newer specific or 'smart' oestrogens known as Selective Oestrogen Receptor Modulators (SERMs) may alleviate the concerns. These agents are selectively oestrogen agonistic, for example, at the skeleton, while acting as oestrogen antagonists at breast and endometrium. Hence patients do not have cyclical bleeds and initial published reports suggest that the first of the SERMs, Raloxifene, may be at least neutral in terms of breast cancer incidence.

For patients who cannot or should not take oestrogen, the next line of treatment comprises the bisphosphonates.[7] These agents, being derivatives of inorganic pyrophosphate, inhibit osteoclastic bone resorption and hence rebalance bone remodelling. The bisphosphonate Etidronate is taken in a daily dose of 400 mg in a two-week pulse followed by 11 weeks of a calcium supplement after which the

13-week cycle is repeated. Prospective trial work shows an encouraging side-effect profile with this agent and efficacy mainly in the spine. Another bisphosphonate, Alendronate, is now also available and appears to have a particular advantage when bone loss prevention at the femoral neck is required. In contrast to Etidronate, it is given continuously in a dose of 10 mg per day rather than cyclically. Care has to be taken to prevent the reported adverse effect of ulceration of the lower esophagus. Thus Alendronate is taken with plain water with the patient in, and remaining in, an erect position for 30 minutes thereafter.

Calcitonin, produced by the C-cells of the thyroid, inhibits osteoclastic bone resorption and has found a role in the prevention of spinal bone loss in postmenopausal women. It is less effective, however, at other sites and doubt remains about its true effect upon fracture rates.

Vitamin D (1,25 dihydroxycholecalciferol) may be used by injection and will prevent spinal bone loss but should probably be used only in the hospital setting where the advent of such adverse effects as hypercalcaemia can be readily detected.

NON-PHARMACOLOGICAL MANAGEMENT

Diet

Whatever treatment is used it should be backed up by sensible advice on diet and exercise. Postmenopausal women need about 1,500 mg of calcium per day to remain in balance and 1,000 mg daily if they are receiving HRT. The mainstay of calcium intake remains dairy products: for reference, a pint of semi-skimmed milk contains around 740 mg of calcium. The skimming process, contrary to the general view of the UK population, does not deplete milk of calcium. If dietary calcium cannot be advanced to the desired level then supplementary calcium can be prescribed. This may be combined with vitamin D in a dual preparation - if the practitioner suspects that the patient is D-deficient. Calcium plus vitamin D should be routinely considered for prescription to elderly patients in institutions where vitamin D deficiency is prevalent.

Exercise

Weight-bearing exercise is essential for bone health as is evidenced by the acute bone loss found in astronauts after prolonged spaceflight. Programmes of exercise in the elderly are associated with increased bone density but maintaining such activities is difficult for patients who may have poor visual acuity and neuro-muscular co-ordination. General advice such as country walking, dancing (particularly of the Scottish country variety), and weight-bearing aerobics should be advocated when appropriate.

Preventing falls

Finally, falls are frequent in the elderly and the ultimate defence against fractures, with related significant morbidity and mortality, is maintainance of visual acuity and their avoidance of medications which may induce drowsiness or neuro-muscular inco-ordination. Potential hazards in the home which could precipitate a fall should be removed. Hip protectors should soon be available, which will take and disperse the kinetic energy of the fall which would normally have been absorbed by the trabecular network of the femoral neck.

CONCLUSION

The loss of trabecula at the key sites of hip, vertebral body and radius, deprives the bone of its great strength and ability to dissipate applied forces, and is at the very heart

of the problem which is caused by osteoporosis. The visualisation, preservation and, if possible, restoration of the trabecular architecture of bone is thus our central goal. However, efforts to reduce the present incidence of osteoporosis-related fractures will only bear fruit when the physician has at his disposal a precise, accurate and low-cost means to diagnose osteoporosis before, rather than after, the first fracture, backed up by more acceptable and efficacious interventions which are safe in the long term.

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