Changing perceptions in osteoporosis

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A recent meta-analysis of 11 separate study populations and over 2000 fractures concluded that bone mineral density "cannot identify individuals who will have a fracture."¹ So why do we measure it? The question is worth asking when the number of dual energy x ray absorptiometry machines installed in the United Kingdom exceeds 130 (National Osteoporosis Society, personal communication), and the number of Medline citations incorporating the term dual energy x ray absorptiometry has grown from 26 in 1988 to 464 in 1997. The concept of "fracture threshold" has led to the recommendation that preventive treatment be given to women once their bone density lies (arbitrarily) more than 1 SD below the mean for premenopausal women—a state of osteopenia, according to the WHO definition. But should we be managing osteoporosis by numbers?

Osteoporosis and osteomalacia

Bone comprises a matrix framework on which mineral is deposited. Osteoporosis is caused by the disintegration of the matrix, and osteomalacia by a failure to mineralise it. When mineralised matrix disintegrates, calcium is inevitably lost. The negative calcium balance observed with matrix loss gave rise to erroneous beliefs that the calcium requirements of postmenopausal women were higher than those of premenopausal women and that osteoporosis could be prevented by calcium supplementation.² Calcium is crucial during the development of bone, but it cannot replace disintegrating matrix or prevent its loss.³ As Heaney has pointed out, calcium is a nutrient and not a drug, and the only disorder it can be expected to alleviate is calcium deficiency.⁴ What is more, excess calcium supplementation will suppress the secretion of parathyroid hormone and slow the natural turnover of bone. "Fossilised" bone is at risk from microfractures. Calcium intakes of between 1 g and 1.5 g daily, commonly recommended in postmenopausal women, are associated with an increased rather than decreased risk of fracture.⁵ Preventing osteoporosis does not depend on calcium, but rather on preserving bone matrix, a living tissue whose structure, strength, and integrity depend, in turn, on fine control of its turnover.

Bone turnover is maintained by two groups of cells—osteoclasts, which dig pits in mineralised matrix, and osteoblasts, which refill the pits. Osteoclastic activity is constrained by the action of sex steroids, and coordination with the osteoblasts is normally maintained such that there is no net change in bone mass

Summary points

Bone densitometry cannot identify people who will sustain osteoporotic fracture

Bone density changes little with antiresorptive treatment (hormone replacement therapy and bisphosphonate drugs), whereas bone turnover falls dramatically

Bone turnover may be the responsive element in treatments to prevent osteoporotic fracture

Antiresorptive treatments prevent fracture, regardless of whether they are given at the menopause or decades later

Since frequency of impact, which rises exponentially with age, is the main risk factor for fracture, treatment should be focused on infirm older people, irrespective of their bone density

during early adult life. After the menopause, circulating oestrogen concentrations fall rapidly and osteoclastic activity accelerates, outstripping the attempts of osteoblasts to keep pace. The net result is bone loss which, over a period of years, may amount to 20% or more of the skeleton.

Effect of antiresorptive drugs

The widespread view that treatment with antiresorptive drugs restores lost bone, and that the increase in bone density observed is responsible for the subsequent reduction in the fracture rate, needs careful rethinking.⁶ There is no evidence that treatment for osteoporosis restores bone, although (unlike calcium supplements) antiresorptive drugs undoubtedly prevent its further loss. The small increases in bone mineral density gained during the early years of treatment with hormone replacement therapy or bisphosphonate drugs soon level off,⁷ and probably reflect no more than the filling by osteoblasts of the myriad pits dug before treatment by uncontrolled osteoclasts.^{7, 8} The challenge to the view that there is a causal relation between bone mineral density and risk of fracture lies in the results of large, placebo controlled, double blind, multicentre trials of bisphosphonate drugs (even those

conducted in ageing women with established osteoporosis). These show a reduction in the risk of fracture at the hip and spine of more than 50%, but an increase in bone mineral density at these sites of only 5-8%,⁹ and even less in earlier studies of spinal fracture.⁷ It is difficult to attribute such a spectacular clinical result to such a small increase in bone mass.

Factors in fracture risk

Hui et al constructed a family of curves relating fracture risk to bone density in different age groups. For the same bone density, the risk of fracture rose eightfold to 10-fold from age <45 years to ≥80 years.¹⁰ In a sample of 5800 Dutch men and women over 55 years of age, the risk of hip fracture rose 13-fold with age, to which the decrease in bone density contributed only 1.9 in women and 1.6 in men.¹¹ These are important observations, because they suggest that something very important in the ageing process influences fracture risk independently of bone density.

Apart from further undermining the validity of bone density as a surrogate for individual fracture risk and its clinical use in identifying those to whom treatment should be given, the observation calls for an explanation. One obvious mechanism is that ageing people fall more frequently and, for a given bone density, sustain fracture more often as a result. Fractures seldom occur without some impact, however fragile the bone, but there may be an additional and more subtle explanation to account for the differences in risk, one which can reconcile the data from clinical trials on fracture risk, bone density, and bone resorption.

It is intuitively likely that bone depends for strength more on its architecture than on its mass. Bone in a younger person is structurally normal, whereas in ageing people its architecture is compromised in two ways. Firstly, the progressive erosion of trabeculas will leave them weakened and, in some cases, disconnected.⁷ Microscopy shows that trabecular erosions and disconnection cannot be reversed by treatment.¹² Secondly, and possibly more importantly, the rate of bone turnover in women who are deficient in oestrogen will inevitably be higher, mass for mass, than in women who are oestrogen replete. If a bolt or two at a time were removed from a cantilever bridge for replacement, architectural strength might not be affected—but if a thousand were removed at one time (a high turnover state), architectural strength could be compro-

mised critically, with little loss in mass. Fractures occur in situations in which high bone turnover is combined with frequent impact. Bone density does not contribute greatly to the individual's risk.

While measurements of bone density emphasise how little bone is regained during antiresorptive treatment, measures of matrix loss show a dramatic and immediate slowing of bone turnover. In postmenopausal women, N-telopeptide type I collagen (a marker for osteoclast activity) fell from 3 SD above the mean to the premenopausal mean within one month of starting treatment, an effect which remained throughout the 15 month study.¹³ The bone specific alkaline phosphatase value (a marker for osteoblastic activity) showed a similar pattern within six months (the delay probably contributed to the 5% increase in spinal bone mass observed over the study period). The fossa intervention trial (FOSIT) observed over 1000 postmenopausal women with low bone density in a placebo controlled trial of alendronate that lasted more than 12 months. It showed an 80% reduction in the bone resorption rate in relation to increases in bone density of 5% at the lumbar spine and just 2% at the neck of the femur.¹⁴

Critics have pointed out that markers of bone turnover are "poorly predictive of bone mineral density ... and cannot be used to diagnose osteoporosis or to select patients for subsequent densitometry," but this is to miss the point.¹⁵ If the modest gain in bone density seen with treatment is insufficient to account for the substantial reduction in fracture risk, a state of high bone turnover, rather than its prevailing mass, may be the responsive element in fracture prevention, no matter at what age it is encountered. The clinical implications are important, as there is no evidence that bone density identifies those people who will sustain a fracture, but abundant evidence that restoring bone turnover to normal values universally reduces the risk. A switch in emphasis from bone density, which declines irreversibly, to bone turnover, which rises, but is fully reversible, makes reducing the risk of fracture a viable consideration at any age after the menopause.

A fall in bone mass, erosion of trabeculas, and ultimately their loss of connectivity must, in themselves, render bone progressively more fragile. However, the evidence cited suggests that fracture risk can be reduced appreciably, even in older women who are already osteoporotic, and without a noticeable restoration of bone mass. The widely held notion that it is too late to treat women with established osteoporosis because bone cannot be restored once it is lost is flawed because bone density and fracture risk are poorly correlated and a high turnover of bone can be normalised at any age or bone density. Bone densitometry might arguably have only a limited role in strategies to prevent osteoporotic fracture.

If high bone turnover rather than low bone density is the major component of fracture risk, antiresorptive drugs should reduce the risk of fracture to the same extent at any age after the menopause, independently of bone density, and when they are stopped their protective effect should be lost before bone density decreases. A recent report by Michaelsson et al provides the first evidence that bears out both these predictions.¹⁶ In a large, population based, case-control study, hormone replacement therapy reduced the risk of hip fracture to the same extent, whether treatment

Healthy, dense bone

began at the menopause or decades later. After hormone replacement therapy was stopped, protection against fracture fell rapidly in relation to the interval since it was last used, and became statistically insignificant after five years.

In 1995, it was claimed that "it is now possible to accurately determine individuals' risk of osteoporosis, and to monitor their response to treatment, by means of bone densitometry."⁷ In the light of current understanding, this is probably not the case. People who will sustain a fracture cannot be identified by bone densitometry, and if bone turnover is the key responsive element in treatment, measures of bone resorption rather than of its density should be the focus of technical developments in monitoring response to treatment.

Programmes for preventing osteoporotic fracture

How much, then, can we be certain of in formulating programmes for the prevention of osteoporotic fracture? We know that antiresorptive drugs taken at the time of the menopause will maintain bone density for as long as they are continued. However, we also know that without them few women sustain fractures before the age of 65 years, probably because they tend not to fall. So has anything been gained in prescribing treatment during 15 years of low fracture risk? Certainly, the NHS can afford neither to screen the perimenopausal population nor to treat blindly. We also know that antiresorptive drugs reduce the risk of fracture equally at any age after the menopause, and that this protection is lost rapidly when they are stopped. Finally, bone density benefits little from antiresorptive agents, while bone turnover returns to its premenopausal state.

If bone density determination cannot distinguish between those who will and will not sustain osteoporotic fractures, it has no place in selecting people for prophylaxis—notwithstanding recent Department of Health guidelines.¹⁷ Current knowledge indicates that prophylaxis should be targeted not at maintaining bone

density throughout menopausal life but at restoring normal bone turnover in those who, for whatever reason, become infirm and at greatest risk of impact. Such an approach to the prevention of osteoporotic fracture would be evidence based, could be budgeted for, and would rationalise management of the individual patient—something that treatment by numbers does not.

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Commentary: Bone density can be used to assess fracture risk

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Wilkin identifies two areas of weakness in the use of bone mineral density measurements. Firstly, he argues that the risk of fracture cannot be predicted from someone's bone mineral density as the relation between the two described in cohort studies is too weak.¹ Secondly, he argues that bone mineral density cannot be used as a surrogate for fracture risk in clinical trials as the relation between a change in density and a change in fracture risk is not as predicted from these cohort studies.¹

I believe that it is reasonable to use an individual's bone mineral density to assess the risk of osteoporotic fracture and to make decisions about treatment with antiresorptive drugs. The relation between bone mineral density and fracture is analogous to that between blood pressure and stroke, and it is just as strong. The problem with bone mineral density has arisen when it has been used to diagnose osteoporosis. This approach raises a

risk factor for fracture to the status of a diagnostic criterion, and ignores the importance of other determinants of bone strength and of factors that increase the risk of falls.² Low bone mineral density is one of the strongest risk factors for osteoporotic fracture. Nonetheless, it is preferable to use this together with other predictive factors that are common and easy to ascertain, such as low body weight (<58 kg), current smoking, a first degree relative with low trauma fracture, and personal history of low trauma fracture.³

An increase in bone mineral density of 5-10% is commonly reported for antiresorptive treatments for osteoporosis, such as hormone replacement therapy and bisphosphonate drugs. The relation between bone mineral density and fracture risk provides a prediction that the reduction in fracture should be about 25%—yet it is closer to 50%.² Wilkin proposes that since

Osteoporotic bone

the change in bone mineral density only partly explains the change in fracture risk, these antiresorptive drugs protect against fracture by reducing the turnover rate of bone.

The importance of a high rate of bone turnover as a risk factor for fracture has been considered by others. Riggs et al, using data from their clinical trial with hormone replacement therapy, concluded that an increase in bone density and a decrease in bone turnover at the spine had approximately equal effects in reducing the risk of spinal fracture.⁴ Parfitt proposed that antiresorptive treatment reduces the rates of bone remodelling, and since these remodelling sites act as stress risers and promote microfractures, their reduction lowers the risk of fracture.⁵ Wilkin is therefore correct to say that the change in bone turnover resulting from antiresorptive treatment may reduce the risk of fracture. The practical consequence of this is that it is reasonable to use markers of bone turnover to monitor treatment.

However, in using these markers in clinical practice, care needs to be taken to minimise their variability.⁶

This marker hypothesis cannot be the entire explanation for the unexpected relation between a change in bone mineral density and a reduced risk of fracture. Treatment with alendronate results in the hypermineralisation of bone tissue. This may change the biomechanical properties of bone⁷ and explain the increase in bone mineral density seen in the third year of alendronate treatment.⁸ Parathyroid hormone treatment increases bone density and turnover, yet it reduces the risk of spine fracture.⁹ We still have much to learn about the mechanism by which treatments for osteoporosis reduce the risk of fracture.

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The World Bank and world health

Changing sides

Kamran Abbasi

"Masters of illusion" is how science writer Catherine Caulfield describes the World Bank, and she writes: "There is much truth in the saying that development is largely a matter of poor people in rich countries giving money to rich people in poor countries."¹ The bank has been highly criticised and has many staunch opponents, but in recent years its public image has softened, and it has become a powerful player in international health.

Methods

For these articles, which attempt a critical portrayal of the bank, I visited its headquarters in Washington, DC, and interviewed leading policy makers, including the former director of the health, nutrition, and population sector, Richard Feacham, as well as the World Bank's vice president for Africa, Callisto Modavo. I interviewed bank employees and visited bank projects in Bangladesh, India, and Pakistan, where my fluency in the local

Summary points

The World Bank's aim is to reduce poverty by investing in people

The past decade has seen it change image from uncaring bully to compassionate stakeholder, focusing on health

It has displaced the World Health Organisation as the major influence behind health policy in poor countries because of its greater funding power

Critics argue that the World Bank and International Monetary Fund increase the debt burden of those countries least able to pay, and that debt relief would be the best way to eradicate poverty

This the first in a series of six articles examining the World Bank's role in international health

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