Fracture risk reduction: more than increasing BMD?

All of the currently available treatments for osteoporosis are capable of at least halting a decline in Bone Mineral Density (BMD) and some, such as the newer bisphosphonates and teriparatide, are capable of increasing it significantly. In this article, Dr Frazer Anderson discusses the question of whether reducing fracture risk is dependent on more than just increasing BMD.

The diagnosis of osteoporosis has been based around Bone Mineral Density (BMD) assessment from its earliest recognition as a cause of fracture, and Dual X-ray Absorptiometry (DXA) is widely used to measure this. There is no qualitative difference between a radiologist’s comment that ‘the bones appear osteopenic’ and the impressively detailed printout from a modern fan-beam DXA scanner. However, the increase in precision from DXA scanners has transformed the usability of BMD in clinical practice. Bones can ‘appear osteopenic’ for many reasons – film exposure, obesity, ascites – but a DXA result gives us a repeatable basis for our treatment decisions. It is also approved by the World Health Organization (WHO) and National Institute for Health and Clinical Excellence (NICE).

In addition, the results from a DXA scan in treatment-naïve patients are as predictive of fracture risk as blood pressure is of stroke risk. Also DXA availability has made osteoporosis real to doctors and budget-holders across the Western world. But as use increases, a question mark is being raised about its correct use in clinical practice – as a tool is only valuable if you use it to do the right job.

Measuring bone strength
Bone is a complex, dynamic material with remarkable strength for its weight. This strength is only partly determined by bone mineral content. Other factors such as protein quality, microarchitecture, bone remodelling and simple physical shape affect fracture risk substantially. Unfortunately, measuring these other factors has tended to be either technically challenging or simply not practical. Any valid measure of bone protein quality still eludes us and bone shape – hip axis length or femoral neck-shaft angle, for example – is difficult to measure reproducibly because minor variations in patient positioning cause big changes in results. However, there is considerable progress in the measurement of bone turnover and in assessing bone microarchitecture.

Physical structure of bone
The structure of our bones is the product of half a billion years of vertebrate evolution to produce the lightest skeleton that can cope with our lifestyle. If our bones were solid lumps of mineral, they would either be unfeasibly heavy or uselessly fragile. Trabecular bone in particular is a miracle of biological engineering, with countless thousands of tiny plates and struts supporting each other along lines of force to give strength, resilience and...
slight deformability using the minimum amount of material. This intricate structure takes quite a battering during normal physical activity and although trabecular bone makes up only about 20 per cent of the skeleton, at least 80 per cent of bone turnover takes place here as bone cells repair the damage.

The main drawback of this complex and active tissue is that progressive loss of bone causes disproportionate loss of strength as trabecular elements are destroyed – rather like dismantling a house of cards one card at a time. Unfortunately osteoporosis does most damage where bone turnover is busiest, so sites with a high content of trabecular bone – vertebrae and the ends of long bones – are inevitably the worst affected. This is why these areas are the sites of the ‘classic’ osteoporotic fractures. Thanks to recent advances in imaging technology such as micro-computed tomography scanning, it is now much easier to appreciate the importance of structural deterioration and the effect of drugs for osteoporosis on bone microarchitecture.

There is one more important factor to consider. Even when new bone is of good quality, it has to be laid down in the right place. For engineering reasons, a wide thin-walled tube is stronger than a narrow thick-walled one, even when they contain the same total amount of material. Consequently, bone laid down subperiosteally contributes more to strength than bone laid down in the endosteal region. We are just beginning to appreciate that drugs for osteoporosis differ in this respect.

### Bone turnover

About three per cent of our skeleton is undergoing bone remodelling – removal and replacement of worn-out bone – at any one time. The process is ‘coupled’ so that rates of removal and replacement are precisely matched, although it takes many months for new bone to become fully mineralised. Biochemical markers of bone turnover have been available for nearly 20 years, although the earlier markers were hard to measure and prone to interference by dietary intake. The newer markers such as pyridinoline and telopeptide assays are more reproducible and highly specific to bone. Their place in clinical practice remains limited mainly by a lack of agreement on how they should be used, but they have given us valuable insights into the effect of antiresorptive drugs on fracture risk.

Firstly, it is clear that any factor that increases bone turnover or uncouples formation from resorption drastically increases fracture risk for a given BMD. This effect is most clearly seen with the accelerated bone turnover in menopausal women and in patients taking corticosteroids. Secondly, any drug that suppresses bone turnover will reduce fracture risk much more quickly than it increases BMD. This, rather than new bone formation, is the principal mode of action of most
studied this BMD increase was not associated with a reduced fracture risk; indeed, there was a clear excess of fractures in treated patients. Microscopic examination of biopsies from treated patients revealed histologically abnormal bone with poor structural organisation and erratic mineralisation. The gain in BMD was more than offset by the loss of structural integrity.

More recent studies have provided further evidence in support of this. Results amongst patients treated with both risedronate (Figure 1) and alendronate (Figure 2) showed there was no difference in fracture incidence in those who experienced an increase in BMD of 0–3 per cent and those whose BMD increase was =>3 per cent.

Practical implications
The main lesson of the ‘fluoride fiasco’ was that the only meaningful measure of a drug’s usefulness as a treatment for osteoporosis is its effect on fracture risk. Recent work suggests that increase in vertebral BMD accounts for only 18 per cent of the reduction in vertebral fracture risk with bisphosphonate treatment – the rest must be due to effects on bone turnover, structure, and perhaps other properties that we do not yet understand. Just because one drug increases BMD more than another we cannot assume that it has a greater effect on fracture risk.

We measure BMD for two reasons: firstly...
because we can measure it and secondly, because we can do something about it. All of the currently available treatments for osteoporosis are capable of at least halting a decline in BMD and some, such as the newer bisphosphonates and teriparatide, are capable of increasing it significantly.

Many specialists perform a repeat DXA scan after starting treatment for osteoporosis in some patients and regard a BMD increase as proof of response. This type of qualitative measurement is reasonable for selected patients, but it is a slow process – the interval between scans must be 18–24 months – and it is also not very sensitive. It makes sense to reserve re-scanning for unusual or complex cases.

In all other circumstances, BMD measurement is a tool for diagnosing osteoporosis, not for quantifying response to treatment. This is as true in multinational drug trials as it is in individual patients. We cannot easily measure the other properties of bone in clinical practice and although there is interesting evidence that some drugs have beneficial effects on bone structure and microarchitecture, this is much less important than proof of fracture prevention.

NICE recommends bisphosphonate therapy as first-line treatment for the secondary prevention of osteoporosis\(^1\). Of the bisphosphonates there is clinical trial evidence of both vertebral and non-vertebral fracture reduction for risedronate and alendronate\(^2\). Teriparatide is recommended as second-line therapy for women over 65 years with severe osteoporosis who are either unresponsive to or intolerant of bisphosphonates. Raloxifene is also offered as an alternative in women intolerant of bisphosphonates, although it has not been shown to prevent non-vertebral fractures.

The appraisal process for strontium ranelate is not yet complete, but the provisional recommendation in the NICE Appraisal Consultation Document is that it will fit in as the ‘first alternative’ to bisphosphonates, displacing raloxifene to third choice.

**Conclusion**

BMD measurement by DXA is a tremendously powerful diagnostic tool in osteoporosis, with a predictive accuracy for future fracture comparable to that of hypertension for stroke.
However, it is not particularly useful for monitoring response to treatment in routine practice as treatment takes years to produce significant changes in BMD. Moreover, the effect of drugs on fracture risk is only partly mediated through BMD change. Treatment choice for patients with osteoporosis should therefore be based mainly on published evidence of fracture risk reduction. □ GM

Conflict of interest: Dr Anderson has previously received writer’s and speaker’s honoraria from the Alliance for Better Bone Health, Merck & Co, Eli Lilly, GlaxoSmithKline, Roche Pharmaceuticals, Servier Laboratories, Shire Pharmaceuticals and Whitehall Laboratories. Dr Anderson has no shareholding or other financial interest in any company

References
12. NICE FAD osteoporosis secondary prevention July 2004

Key points

- BMD measurement is an excellent tool for diagnosing osteoporosis but a poor guide to treatment efficacy.
- Bone strength depends on microarchitecture, structure and turnover as well as density.
- Treatments for osteoporosis vary widely in their effect on these other factors.
- The only important measure of efficacy is fracture reduction.
- The effect of drugs on fracture risk is only partly mediated through BMD change.
- Treatment choice for patients with osteoporosis should therefore be based mainly on published evidence of fracture risk reduction.