

# Bone failure or osteoporosis

## What's in a name?

**CHRIS WHITE** MB BS, PhD, FRACP

**JOHN EISMAN** MB BS, PhD, FRACP, AO

*In clinical practice we know when an organ system is not working properly and we call it by its appropriate name: organ failure. The term is straightforward and treatment follows accordingly. A similar approach is needed in the way we approach osteoporosis. By introducing the term 'bone failure' and distinguishing between osteoporosis as a risk factor and bone failure as a disease, we set the stage for better clinical management.*

### Key points

- **The way we name something defines the way we think about it and prioritise our investigations and treatment.**
- **Osteoporosis is used to describe both a disease and a risk factor, which causes confusion. Low bone density defines osteoporosis but it is also a risk factor for osteoporotic fracture.**
- **When 'osteoporosis the disease' becomes 'bone failure' we gain the ability to distinguish between the risk factor and the disease.**
- **Bone failure is an accurate term for the clinical condition where a bone fractures, either spontaneously or under circumstances when we would not expect it to do so.**
- **Recognising the first bone failure event is key and secondary fracture prevention is crucial as we live longer lives.**

ENDOCRINOLOGY TODAY 2015; 4(4): 29-32

Associate Professor White is the Head of the Department of Endocrinology and Co-director of SEALS Clinical Chemistry and Endocrinology at Prince of Wales Hospital, Sydney; Director of the Centre for Osteoporosis and Bone Research at Royal Hospital for Women, Sydney; and Conjoint Associate Professor at The University of New South Wales, Sydney. Professor Eisman is the Director of Clinical Translation and Advanced Education at the Garvan Institute of Medical Research, Sydney; Staff Specialist in Endocrinology at St Vincent's Hospital, Sydney; Professor at the School of Medicine Sydney, University of Notre Dame Australia; and Conjoint Professor of Medicine at The University of New South Wales, Sydney, NSW.



**T**rained as scientists, doctors are skilled at categorising and comparing. Differences are accorded significance and pursued, and disease is often categorised as a dichotomous variable. Along the same lines, when it comes to treatment, therapies are either proven effective or not. Overall, when there can be only two outcomes, this model serves medicine well. Although there can be grades of severity and degrees of response, it is nonetheless the goal of oncologists and haematologists to cure patients of cancer and of surgeons to remove the inflamed appendix. However, where disease has a continuous spectrum our desire to categorise and compartmentalise must be adapted. We do this by establishing thresholds at which disease is defined as either present or absent, such as in the diagnosis of hypertension.

Sometimes we even create intermediate categories between the presence and absence of disease, as reflected by the terms subclinical (e.g. subclinical hypothyroidism), precursor and prodrome. A good example is defining diabetes mellitus, impaired glucose tolerance, impaired fasting glucose and normal responses to a standardised glucose load.

In osteoporosis medicine, we mimicked this when establishing thresholds at which osteoporosis, osteopenia and normal bone were defined based on an arbitrary T-score.<sup>1</sup> Early discoveries in the field advanced in this dichotomous fashion until it became apparent that it was not just the last fracture that mattered but as much the ability to predict the likelihood of having the first or, lamentably, the next fracture.

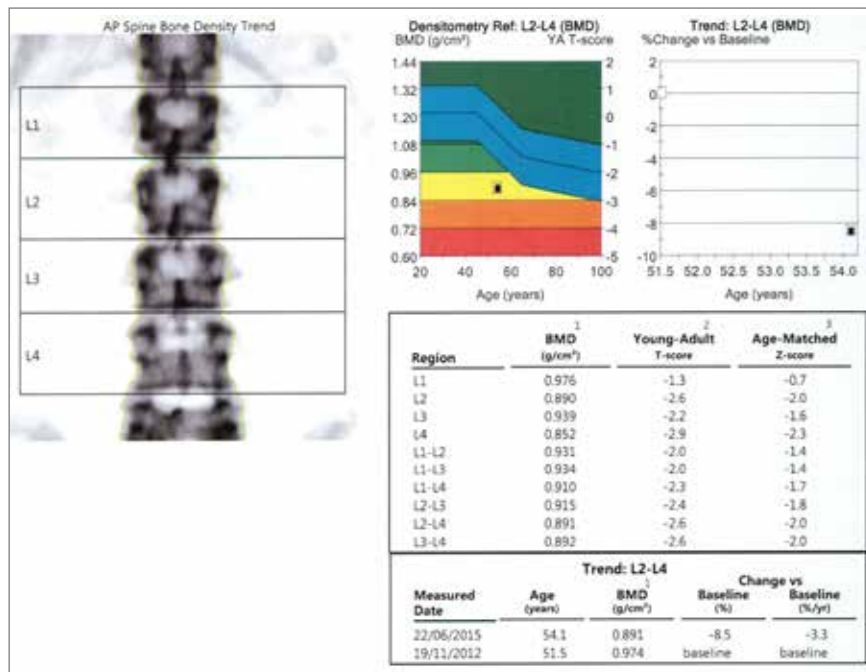


Figure 1. A 54-year-old woman's bone mineral density results showing osteoporosis.

### Managing osteoporosis risk as we live longer

Risk cannot always be sensed, it is not necessarily a disease and nor is it dichotomous. Given the reality that we are living longer, risk cannot be ignored. We are long past a time when the risk of dying from something else was greater than the risk of living long enough to develop osteoporosis because the diseases that used to kill us no longer do.

Today we can expect to survive to experience a new constellation of age-related diseases such as osteoporosis, which represent not so much a tsunami gathering in the distance but a cliff towards which we march our blissfully unaware patients (and ourselves). However, managing vascular, metabolic and malignant diseases (or their risk factors) to live a life in old age crumpled by osteoporosis is misguided and does not have to be the case today.

### Tools for assessing the risk of osteoporosis

Over the past decade, a number of risk assessment tools have revolutionised the way we think about osteoporosis and increased our ability to predict an individual patient's fracture risk.<sup>2,3</sup>

Although the T-score remains an important component of risk assessment, it is by no means the only tool used today (Figure 1). Factors including a patient's age, sex, the number of previous falls and previous fractures of major axial and appendicular bones can reliably be used to predict a patient's risk of hip and any fragility fractures.

The two most widely available risk calculators, the Fracture Risk Assessment Tool (FRAX) and the Garvan Fracture Risk Calculator, differ in the weight they attribute to these risk factors but one is not necessarily superior to the other. FRAX limits the risk to fewer sites and does not include falls or the number of previous fractures although the model does include extra categorical assignments for corticosteroid therapy, rheumatoid arthritis, alcohol intake, current smoking and a parent with a hip fracture. FRAX also adjusts, possibly overadjusts, for risk of death. Garvan risk estimates are approximately twice those obtained using FRAX and have been validated in international cohorts.<sup>4,5</sup> Neither fracture risk calculator has been validated in the lower risk groups of younger premenopausal women under the age of 40 years (FRAX) or 50 years (Garvan), nor for some individuals

with some increase in risk, such as patients with diabetes.

### Changing the approach to treatment of osteoporosis

Although our appreciation of an individual patient's risk of fracture has changed and broadened, treatment considerations remain dichotomous. PBS criteria, based on population health economics and not individual patient risk, arbitrarily restrict available therapies primarily on the basis of prior low-trauma fractures. It is only in a much smaller group of patients that bone mineral density (BMD) and age or corticosteroid use are included as criteria for access to PBS subsidies.

We need to actively consider the logical thresholds of risk at which effective and well-tolerated drugs would be made available and should be used, independent of these dichotomous criteria. At present no such consensus has been reached. However, as a baseline for discussions with patients and health service providers, Garvan risk assessment using current PBS criteria for reimbursement equates to a 10-year risk of hip fracture in the range 3 to 9% and of fracture at any major site in the range 14 to 26%.

A factor complicating funding decisions about reimbursement for therapy is that to date none of the randomised controlled trials proving treatment efficacy have used the FRAX or Garvan risk calculators for recruitment. This is because the two risk calculators were published after most of the studies were either published or had begun enrolling patients.

Logical explanations of absolute risk should also underpin the discussions with patients about whether a drug should be used, their reasonable concerns about efficacy and the currently overblown concerns about side effects.

For a patient who falls within or beyond the above risk ranges, yet doesn't meet the current criteria for PBS reimbursement (e.g. a 67-year-old woman with a BMD T-score of -3.5 and a 10-year risk of hip fracture of 11% and of any major fracture 27%) then the minimum out-of-pocket expense for oral or parenteral therapy would be between \$A120 and \$A606 per annum.

## Changing the way we talk about osteoporosis

As clinicians we are experts at recognising organ failure. Arguably we learn more about how the human body functions from the study of its diseases. Indeed much clinical knowledge has been determined in this 'retrograde' fashion. An impaired, dysfunctional myocardium creates a constellation of clinical signs and symptoms that we learn to recognise as heart failure. In the same way, we learn how to diagnose liver failure, renal failure and dementia.

Imagine a kyphotic woman walking with a frame or stick, her head awkwardly if not painfully hyperextended, having had a pin inserted in her hip after a fall resulted in a fractured neck of femur. This is a clinical picture we would immediately associate with a syndrome of bone that has failed. Bone failing spontaneously or in circumstances that we would not expect it to fail is a disease, and that disease has a name: currently osteoporosis. However, osteoporosis is also still confused with risk per se.

Medical science, initially limited to recognising diseases as they occurred, has advanced to identify modifiable factors that predispose to the onset of disease. This hopefully allows us to intervene and prevent, or at the very least slow, the progress towards organ failure.

Hypertension, in addition to several other disorders, is a risk factor for stroke, and hypercholesterolaemia is a risk factor for coronary artery disease. Yet we do not call hypertension 'a stroke', nor do we call high cholesterol 'an acute coronary syndrome'. To do so would be inherently confusing and unworkable. Hypertension and hypercholesterolaemia are important quantifiable and remediable risk factors for events that will lead to organ failure, but they are recognisable and distinct entities.

Low BMD is a risk factor for osteoporosis but is also part of the definition, a very confusing situation. Equally, although a risk factor for fracture, BMD is by no means the only one. Importantly, not all patients with low BMD experience fractures in the near future. Perhaps more importantly, not all patients who experience a fracture have a BMD more than 2.5 standard deviations (SD) below that of young normal adults. Although the risk of sustaining

a fracture is higher when BMD is below this threshold, the larger number of patients sustaining a minimal trauma osteoporotic fracture have osteopenia rather than frank osteoporosis.<sup>6</sup> In fact the relationship between BMD and fracture is a continuous exponential one, without any inflexion of increase in risk at any particular level of BMD. As a result, more people suffer fractures at relatively higher BMD simply because there are so many more people above this arbitrary cut-point, albeit each with somewhat lower absolute risk. Thus we have the confusing contradiction that many, if not most, patients with osteoporotic fractures do not have osteoporosis (by BMD). To add to the confusion, when vertebrae fail and fracture by compression, the lesser amount of bone is compressed into a smaller space, leading to a spurious increase in apparent BMD that could lead to an osteoporotic vertebra being mistakenly categorised as osteopenic or even normal (Figure 2). If this can be confusing to clinicians and general practitioners who do not routinely work in the field of osteoporosis medicine, imagine the confusion for our patients.

## Changing the names we use to improve communication

As communicators, we have the responsibility of clearly and concisely conveying complex physical and medical concepts to our patients as well as to the next generation of clinicians and investigators. To do so obligates us to classify a disease and its risk factors with clarity and precision. Names are important because they must illuminate not obfuscate.

Why then in the field of osteoporosis medicine do we walk in a minefield of misnomers? BMD is not density (but mass per area), and osteoporosis is both a disease and a risk factor. To be fair, it could be argued that at the time that BMD was being investigated for its ability to predict fracture it was a novel concept to measure a risk factor that was diminishing rather than increasing. Elevated blood glucose, blood pressure or cholesterol levels could theoretically reach any peak level well above that which was considered normal, but no patient could have no bone. There had to be a threshold beyond which the skeleton could no longer support itself. However, investigators have



Figure 2. Vertebral crush fractures (arrows).

recently shown that brain glucose hypometabolism may have the highest sensitivity and specificity for predicting the subclinical onset of Alzheimer's disease.<sup>7</sup> It would be surprising if a reduced level of activity on a fluorodeoxyglucose positron emission scan is called 'dementia'. Yet we call low BMD, which is a risk factor for osteoporosis, the same name as the disease itself. Hence we propose 'bone failure' as a meaningful and accurate term for the clinical condition when a bone fails (fractures) when we would not expect it to do so.

Without convening a major multinational task force to recodify the terms used in osteoporosis medicine, there is one simple thing that practitioners can do today to overcome the impasse and change the way we approach osteoporosis for the immediate benefit of our patients. The term BMD is established after decades of use and, although not strictly accurate, can suffice for the purposes of defining a measurable risk factor for fracture. Similarly the term osteoporosis, as defined by the World Health Organization, is a T-score on BMD by dual x-ray absorptiometry of more than -2.5 (i.e. more than 2.5 SD below the BMD of young normal women) and is entrenched nomenclature. Reimbursement for tests and medications are based on this threshold. To change the name of the

### Cases illustrating the complexity of diagnosis of bone failure and osteoporosis

#### Case 1

A 63-year-old man with three vertebral crush fractures and a total hip BMD T-score of -0.9 (i.e. BMD 0.9 SD below that of young normal men and thus within the young normal range) has bone failure. Even without any fall propensity, his risk of any fragility fracture in the next five to 10 years is 29 to 48%, respectively.<sup>3</sup> Assuming he does not have any reversible secondary factors, such as hypogonadism or coeliac disease, he requires effective treatment with bone-specific medication to attenuate this high risk. He should be treated and meets current PBS criteria for treatment with one of the potent antiresorptive agents (a bisphosphonates or denosumab), which are well tolerated. This will effectively halve his fracture risk.

#### Case 2

A 73-year-old woman without any prior fractures but a BMD T-score of -2.8 (i.e. BMD 2.8 SD below that of young normal women) has osteoporosis. If she has had even one fall in the past year, her risk of a hip fracture in the next five to 10 years is 6 to 12%, respectively, and of any fragility fracture in the next five to 10 years is 15 to 30%, respectively.<sup>3</sup> Although her risk of any fragility fracture is lower than that of the man in case 1, she should also be treated. She also meets PBS criteria for treatment, based on her age and low bone density. She should receive one of the potent antiresorptive agents (a bisphosphonate or denosumab), which are well tolerated. This will effectively halve her fracture risk.

risk factor presents a greater challenge than changing the way we think and talk about the disease.

However, when 'osteoporosis the disease' is called 'bone failure', we gain the ability to distinguish between the risk factor and the disease, which benefits both patients and doctors. Once we separate the concept of osteoporosis from the disease, it becomes easier to interpret BMD and to develop diagnostic and treatment approaches based on risk. It also becomes easier to tailor investigations based on T-scores and Z-scores and the clinical context in which the patient presents, for example exposure to corticosteroids and aromatase inhibitors.

### Bone failure is a clinical diagnosis

Any bone can break, but bone failure is the failure of the skeleton under circumstances in which we would not expect it to fail in a younger healthy individual. A fall, generally from standing height or less, at an earlier time in a patient's life would at most lead to bruising or a soft tissue injury but is now exacerbated by the loss of function arising from fracture. Also the spontaneous loss of integrity of a bone, often vertebral, without any recognisable insult other than weight bearing we take for granted as bone failure (now called osteoporosis).

### Fractures that predict the next bone failure

Not all broken bones are diagnostic of bone failure. Only fractures involving bones at or above the wrist but below the clavicle, three or

more ribs, the pelvis, or femur and lower limb bones down to the ankle (excluding the lateral malleolus in women) represent fractures that predict the next bone failure event.<sup>8,9</sup> As we age, these fractures show an increasingly centripetal and disabling predisposition. In one study of patients presenting with a hip fracture, about half of the women and one-third of the men volunteered the information that they had a prior fracture, and few if any were on any bone-specific treatment.<sup>10</sup> This finding represents so many missed opportunities for prevention of such major, costly, life-changing and potentially life-threatening fractures. Recognising the first bone failure event is key, and secondary fracture prevention is crucial.

### Conclusion

So what is in a name? Overtly or inadvertently, it defines the way we think and prioritise our investigations and treatment of patients. Once we differentiate osteoporosis the risk factor from osteoporosis the disease, it becomes intuitively easier to address osteoporosis as a risk factor for the disease of bone failure (see the Box for case examples). BMD then becomes just one of several risk factors we need to consider when developing a diagnostic and treatment plan for individual patients that is now based on risk. We have to do better than the current data indicate; perhaps 20% of women and fewer than 10% of men get the effective bone-specific treatment that we would rationally suggest in Australia and worldwide.<sup>11</sup> **ET**

### References

1. Kanis JA, Melton LJ, Christiansen C. The diagnosis of osteoporosis. *J Bone Miner Res*. 1994; 9: 1137-1141.
2. Kanis JA, Oden A, Johansson H, Borgström F, Ström O, McCloskey E. FRAX and its applications to clinical practice. *Bone* 2009; 44: 734-743.
3. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. *Osteoporos Int* 2008; 19: 1431-1444.
4. Langsetmo L, Nguyen TV, Nguyen ND, et al. Independent external validation of nomograms for predicting risk of low-trauma fracture and hip fracture. *CMAJ* 2011; 183: E107-114.
5. Pluskiewicz W, Adamczyk P, Franek E, et al. Ten-year probability of osteoporotic fracture in 2012 Polish women assessed by FRAX and nomogram by Nguyen et al. - Conformity between methods and their clinical utility. *Bone* 2010; 46: 1661-1667.
6. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA* 2001; 286: 2815-2822.
7. Mosconi L, Pupi A, De Leon MJ. Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. *Ann N Y Acad Sci* 2008; 1147: 180-195.
8. Bliuc D, Nguyen TV, Eisman JA, Center JR. The impact of nonhip nonvertebral fractures in elderly women and men. *J Clin Endocrinol Metab* 2013; 99: 415-423.
9. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA* 2007; 297: 387-394.
10. Port D, Center J, Briffa NK, Nguyen T, Cumming R, Eisman J. Osteoporotic fracture: missed opportunity for intervention. *Osteoporos Int* 2003; 14: 780-784.
11. Eisman JA, Bogoch ER, Dell R. Making the first fracture the last fracture: ASBMR task force report on secondary fracture prevention. *J Bone Miner Res* 2012; 27: 2039-2046.

COMPETING INTERESTS: None.