Editorial

Recommendations for bone marker standards in osteoporosis: what, why and where to now?

Samuel D Vasikaran[1,2], Cyrus Cooper[3,4] and John A Kanis[5]

[1]PathWest Laboratory Medicine-Royal Perth Hospital, Department of Core Clinical Pathology and Biochemistry, Perth; [2]School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, WA, Australia; [3]MRC Lifecourse Epidemiology Unit, Southampton General Hospital, University of Southampton, Southampton SO16 6YD; [4]NIHR Musculoskeletal Biomedical Research Unit, Institute of Musculoskeletal Sciences, University of Oxford, Oxford OX3 7LD; [5]Centre for Metabolic Bone Diseases (WHO Collaborating Centre), University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK

Corresponding author: Samuel D Vasikaran, Department of Core Clinical Pathology and Biochemistry, PathWest Laboratory Medicine-Royal Perth Hospital, Perth, WA, Australia. Email: samuel.vasikaran@health.wa.gov.au

DOI: 10.1258/acb.2011.010286

Osteoporosis is a major health problem worldwide with a prevalence that is projected to increase further due to the ageing population.[1] It is defined as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk.[2] The World Health Organization diagnostic criterion for osteoporosis is a bone mineral density (BMD) measurement equal to or more than 2.5 standard deviations (SD) below the young female (age 20–29 years) reference mean (T-score ≤ -2.5 SD).[3,4] Whereas osteoporosis is a silent disease, its clinical consequences result from fractures, especially hip fracture, which accounts for the major direct costs. Several highly effective agents have been developed for the treatment of osteoporosis, which have been shown in clinical trials to reduce the risk of fractures. However, in selecting patients for treatment it needs to be borne in mind that the majority of minimal trauma fractures do not in fact occur in those with osteoporosis but in those with osteopaenia, defined as a femoral neck BMD T-score between -1 and -2.5, and normal BMD, defined as a T-score > -1, due to the much higher prevalence of the latter classifications. Apart from BMD, independent contributors to fracture risk include age, gender and a range of clinical risk factors such as prior fractures, parental hip fracture history, body mass index, ethnicity, smoking, alcohol use, glucocorticoid use, rheumatoid arthritis and secondary osteoporosis. The independent contribution of each of these risk factors for fracture has been quantified, permitting the calculation of absolute risk for an individual patient with the FRAX® tool (http://www.shef.ac.uk/FRAX) in order to identify individuals who would best benefit from treatment.[5]

Bone turnover markers (BTMs) in blood and urine have been extensively studied in relation to fracture risk assessment and found to predict fracture risk independently of BMD, but they are currently not included in fracture risk algorithms nor are their use in assessment of patients recommended by many guidelines.[5] Whereas the large biological variations seen in these markers are generally recognized,[6,7] the availability of a number of different markers and their use in different clinical trials and, in many cases, the use of different methods for the same marker, have resulted in the dearth of population-based prospective studies with any single analyte. The lack of data from a large part of the world's populations also limits their international use, with most data coming from Europe and North America. The area where there is most evidence currently available for the use of BTMs in osteoporosis is in monitoring therapy, especially with antiresorptive agents.[8–12] BTMs generally show large and rapid responses to the treatments used for osteoporosis in contrast to the slow and modest increment in BMD. The treatment of postmenopausal osteoporosis with an antiresorptive agent results in an early decrease in bone resorption markers followed by a later decrease in bone formation markers. In contrast, treatment with an anabolic agent such as teriparatide results initially in an increase in bone formation and later in an increase in bone resorption.[13] Changes in BTMs following treatment with antiresorptive agents explain a greater percentage of the fracture risk reduction than does the change in BMD.[11] Also, the effect of change in BTMs is independent of change in BMD. Therefore, there is a sound scientific basis for the use of BTMs in monitoring therapy, although there remains a need for more data in this respect.

A position paper recently released by the joint International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine (IOF-IFCC) Working Group on Bone Marker Standards has highlighted the hiatuses in our current knowledge of the application of BTMs in the management of osteoporosis, and the need to enlarge the experience of the value of BTMs for fracture risk assessment in population-based studies around the world and in monitoring osteoporosis treatment with different agents.[14] A major recommendation of this Working Group is the proposal for the use of one bone formation marker (serum procollagen type I N propeptide, s-PINP) and one bone resorption marker (serum C-terminal cross-linking telopeptide of type I collagen, s-CTX) as reference analytes in clinical trials as well as in observational

studies in order that adequate data be accumulated for their application in clinical practice.[14] Although it is recognized that there is no perfect gold standard marker, the reference standards were chosen based on criteria such as adequate characterization and clear definition of the marker, their specificity to bone and performance in clinical studies, wide availability, biological and analytical variability, sample handling, stability, ease of analysis and availability of method in routine laboratories and the medium of measurement (serum versus urine). Areas that need to be carefully controlled when studying the reference BTMs in future clinical trials include appropriate sample handling, ensuring that BTMs are measured in all available patients in trials and the use of appropriate statistical methods, including an assessment of whether the final BTM level following treatment is a guide to fracture risk. Other possible uses of BTMs which also need further study include the prediction of rate of bone loss, identification of secondary osteoporosis, targeting intervention and improving adherence.

The standardization of measurement of the reference BTMs, which is flagged as a future goal of this working group, should ensure comparability of data across time and space, and help determine universally applicable decision points for each marker. The current lack of inter-laboratory agreement of results for BTMs, even where the same method is used for a particular analyte, is well recognized.[15] This makes it difficult to follow a patient by testing in different laboratories, problematic for multicentre clinical trials and impossible to designate cut-points and decision levels in treatment guidelines.

The adoption of reference BTM standards does not preclude the use of other BTMs in clinical studies. Rather, it provides internal references and the ability to pool studies more easily for meta-analyses both for appropriately powered cohort studies so that BTMs can be considered alongside other risk factors for fracture risk calculations and for inclusion in clinical trials to allow study of the relationship between change in BTM and fracture risk reduction.

In conclusion, the IOF-IFCC's position paper, while highlighting the hiatuses in our current knowledge, supports the role of BTMs in the management of patients with osteoporosis. It identifies areas in which further data need to be accumulated and asserts that the adoption of international reference standards by the clinical and scientific community in the field of osteoporosis research will markedly enhance laboratory consistency and facilitate their inclusion in routine clinical practice.

DECLARATIONS

Competing interests: SDV declares no competing interests. JAK and CC have no competing interests with regard to markers of bone turnover.

Funding: None.
Ethical approval: Not applicable.
Guarantor: SDV.
Contributorship: SDV wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.
Acknowledgements: None.

REFERENCES

1 Burge R, Dawson-Hughes B, Solomon D, Wong J, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 2007;**22**:465–75
2 Consensus Development Conference: diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med* 1993;**94**:646–50
3 Kanis JA, Melton LJ, Christiansen C, Johnston C, Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res* 1994;**9**:1137–41
4 Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ, Khaltaev N. A reference standard for the description of osteoporosis. *Bone* 2008;**42**:467–75
5 Compston J, Cooper A, Cooper C, *et al.* for the National Osteoporosis Guideline Group. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas* 2009;**62**:105–8
6 Vasikaran SD, McCloskey EV, Kahn S, Kanis JA. Intra-individual variation in fasting urinary calcium- and hydroxyproline-creatinine ratios measured in metabolic bone clinic patients as both outpatients and inpatients. *Ann Clin Biochem* 1994;**31**(3):272–6
7 Hannon R, Eastell R. Preanalytical variability of biochemical markers of bone turnover. *Osteoporos Int* 2000;**11**:S30–44
8 Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res* 2003;**18**:1051–6
9 Reginster J-Y, Sarkar S, Zegels B, *et al.* Reduction in PINP, a marker of bone metabolism, with raloxifene treatment and its relationship with vertebral fracture risk. *Bone* 2004;**34**:344–51
10 Sarkar S, Reginster J-Y, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Relationship between changes in biochemical markers of bone turnover and BMD to predict vertebral fracture risk. *J Bone Miner Res* 2004;**19**:394–401
11 Bauer DC, Black DM, Garnero P, *et al.* Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. *J Bone Miner Res* 2004; **19**:1250–8
12 Delmas PD, Munoz F, Black DM, *et al.* The HORIZON-PFT Research Group. Effects of yearly zoledronic acid 5 mg on bone turnover markers and relation of PINP with fracture reduction in postmenopausal women with osteoporosis. *J Bone Miner Res* 2009;**24**:1544–51
13 Arlot M, Meunier PJ, Boivin G, *et al.* Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. *J Bone Miner Res* 2005;**20**:1244–53
14 Vasikaran S, Eastell R, Bruyère O, *et al.* Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 2011;**22**:391–420
15 Seibel MJ, Lang M, Geilenkeuser WJ. Interlaboratory variation of biochemical markers of bone turnover. *Clin Chem* 2001;**47**:1443–50