Editorial

The Role of Biochemical Markers of Bone Turnover in Osteoporosis Management in Clinical Practice

***Samuel D Vasikaran,[1,2] Paul Glendenning,[1] Howard A Morris[3]**

[1]Department of Core Clinical Pathology and Biochemistry, PathWest-Royal Perth Hospital, GPO Box X 2213, Perth, WA 6847, Australia. [2]School of Surgery and Pathology, University of Western Australia, Perth, WA 6009, [3]Hanson Institute, IMVS, Frome Road, Adelaide, SA 5000, Australia.

*For correspondence: Clin A/Prof Samuel Vasikaran e-mail: samuel.vasikaran@health.wa.gov.au

Biochemical markers of bone remodelling have shown promise for over two decades as useful tools in the assessment of patients with metabolic bone disease. Compared to imaging techniques, they are safe, non-invasive, comparatively inexpensive and easily performed. Yet the clinical role of biochemical bone markers remains a controversial subject. The interpretation of values for the individual patient is complex and this is most likely inherent to the complexity of bone metabolism itself. This complexity is increased when taken in conjunction with the variation due to the preanalytical process that must also be taken into consideration.[1] Furthermore, lack of standardisation has resulted in unacceptable inter-laboratory variation in results.[2] While an enormous amount of data has been acquired on the use of bone markers in metabolic and metastatic bone disease, their large-scale use by routine laboratories would potentially be in the management of osteoporosis, a common condition with an increasing prevalence in an ageing population. Yet, most current guidelines on osteoporosis management do not recommend them for routine clinical use, instead, the guidelines largely relegate their use to research and specialist practices.[3-5] Is this situation likely to change in the near future, with the use of bone markers being recommended for routine use? In this issue of the Clinical Biochemist Reviews, Seibel reviews the current state of bone markers with regard to their use in the management of osteoporosis.[6]

Can bone turnover markers assist the clinician to identify patients at greatest risk of fracture? The diagnosis of osteoporosis is based on bone density scanning by virtue of the WHO definition of osteoporosis and patients with a low bone density have increased risk of fracture. However, a considerable body of data indicates that bone markers predict bone loss independent of bone density; individuals with increased bone turnover markers lose bone at a faster rate than subjects with normal or low bone turnover markers.[7-10] Markers of bone resorption seem to be stronger predictors of future bone loss than markers of bone formation, and correlations are stronger in elderly than in younger women.[11-14]

Bone turnover markers, in combination with other risk factors for osteoporotic fracture, may be used to define fracture risk and intervention thresholds. In women with low bone mass, bone turnover markers are independent predictors of fracture risk; vertebral fracture is directly correlated with bone turnover marker concentration and negatively with vertebral bone mineral density (BMD).[15-17] The relative fracture risk, as defined by either low BMD or an increased bone turnover marker, are similar, and increased fracture risk is accentuated when both are present. Thus, in clinical practice, increased bone turnover markers in the presence of a low BMD would favour initiation of treatment for that patient.[2]

In the past, most therapeutic options for osteoporosis involved antiresorptive medications. Now we also have the option of prescribing anabolic agents like injectable recombinant PTH 1-34 (teriparatide) and strontium ranelate. Does this mean that in future we will be able to tailor treatment based on baseline rate of bone remodelling ie those with suppressed bone remodelling being prescribed anabolic agents and those with increased bone remodelling being prescribed antiresorptive agents? The theoretical possibility for this approach has not been tested and will need to be addressed by future clinical trials, although current evidence does not suggest this will be the case.[18] However, some studies do suggest that patients with raised bone markers at baseline respond better to antiresorptive therapies,[19] or that patient stratification by pre-treatment bone marker concentration may make sense from a pharmaco-economic point of view.[18,20]

The most persuasive evidence to date for the use of bone markers is in the area of monitoring of osteoporosis

treatment. The aim of treatment is to prevent fractures. Bisphosphonates**,** oestrogens and raloxifene decrease bone resorption and bone formation markers; strontium ranelate treatment causes a mild reduction in bone resorption markers and a mild increase in bone formation markers; teriparatide increases both bone formation and bone resorption markers. This has been investigated by several studies which have shown that short-term reductions in bone turnover following antiresorptive therapies are associated with subsequent reduction in vertebral and/or non-vertebral fracture risk.[15,21-25] The advantage of using bone markers instead of BMD is that significant changes in bone markers can be observed at three to six months after initiation of therapy allowing early intervention in those who do not show the expected response to check for non-compliance, investigate for secondary causes of osteoporosis and to modulate treatment if necessary. BMD changes on the other hand, may take 18 months to become significant; a long time to wait to detect treatment failure. In fact, fracture reduction occurs before significant changes in BMD can be established. Thus, the reduction in fracture incidence following antiresorptive treatment in clinical trials was seen early, similar to the change in bone markers, whereas the changes in BMD were gradual and later. Not surprisingly, the change in bone markers explains a much greater proportion of reduction in fracture risk than any change in BMD. Taken together, these data suggest that bone markers are arguably better tools than BMD for monitoring antiresorptive therapy although in practice the two techniques would complement each other. Seibel has also described studies which have shown that using bone markers for monitoring osteoporosis treatment can increase compliance and adherence to treatment and improve the effectiveness of the treatment.[26-28] Whether changes in bone turnover during treatment with agents such as strontium ranelate, or teriparatide predict fracture outcomes is presently not clear. Studies have shown that changes in bone markers with teriparatide therapy predict changes in BMD and improvement in bone structure;[29,30] data on fracture prediction should follow. A bone formation marker such as aminoterminal propeptide of type I collagen (PINP) may be a candidate for monitoring teriparatide therapy.[31]

In conclusion, there is a compelling case that bone markers are most useful in at least two areas. In an individual with low BMD, the presence of increased bone turnover markers suggests an increased risk of fracture compared to low or normal bone turnover and may help in the treatment decision for the individual patient. Secondly, bone markers are likely to be useful in the monitoring of a patient receiving antiresorptive therapy, a situation where they are the marker of choice in the first 12-18 months following commencement of treatment. The use of bone markers in other areas will require further data from large clinical trials.

Competing Interests : None declared.

References

1. Seibel MJ. Biochemical markers of bone turnover: Part I: biochemistry and variability. Clin Biochem Rev 2005;26:97-122.
2. Seibel MJ, Lang M, Geilenkeuser WJ. Interlaboratory variation of biochemical markers of bone turnover**.** Clin Chem 2001;47:1443-50.
3. Guidelines for the management of postmenopausal osteoporosis for GPs. The Royal Australian College Of General Practitioners. (accessed June 30, 2006) http://www.racgp.org.au/document.asp?id=14997
4. Management of osteoporosis in postmenopausal women: 2006 position statement of the North American Menopause Society. (accessed June 30, 2006) http://www.menopause.org/psosteo.pdf?bcsi_scan_276FAA45874D151E=1
5. Guideline No 71: Management of Osteoporosis. Scottish Intercollegiate Guidelines Network. (accessed June 30, 2006) http://www.sign.ac.uk/guidelines/fulltext/71/index.html
6. Seibel MJ. Biochemical markers of bone turnover: Part II: Clinical Applications in the Management of Osteoporosis. Clin Biochem Rev 2006;27:123-38.
7. Rosen C, Chesnut CH 3rd, Mallinak NJ. The predictive value of biochemical markers of bone turnover for bone mineral density in early postmenopausal women treated with hormone replacement or calcium supplementation. J Clin Endocrinol Metab 1997;82:1904-10.
8. Chesnut CH 3rd, Bell N, Clark G, et al. Hormone replacement therapy in postmenopausal women: Urinary N-telopeptide of type I collagen monitors therapeutic effect and predicts response of bone mineral density. Am J Med 1997;102:29-37.
9. Christiansen C, Riis BJ, Rodbro P. Prediction of rapid bone loss in postmenopausal women. Lancet 1987;1:1105-8.
10. Christiansen C, Riis BJ, Rodbro P. Screening procedure for women at risk of developing postmenopausal osteoporosis. Osteoporosis Int 1990;1:35-40.
11. Cosman F, Nieves J, Wilkinson C, Schnering D, Shen V, Lindsay R. Bone density change and biochemical indices of skeletal turnover. Calcif Tissue Int 1996;58:236-43.
12. Mole PA, Walkinshaw MH, Robins SP, Paterson CR. Can urinary pyridinium crosslinks and urinary oestrogens predict bone mass and rate of bone loss after the menopause? Eur J Clin Invest 1992;22:767-71.
13. Reeve J, Pearson J, Mitchell A, et al. Evolution of spinal bone loss and biochemical markers of bone remodelling after menopause in normal women. Calcif Tissue Int 1995;57:105-10.
14. Ross PD, Knowlton W. Rapid bone loss is associated

with increased levels of biochemical markers. J Bone Miner Res 1998;13:297-302.

15. Riggs BL, Melton LJ 3rd, O'Fallon WM. Drug therapy for vertebral fractures in osteoporosis: evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. Bone 1996;18: S197-S201.
16. Garnero P, Hausherr E, Chapuy MC, et al. Markers of bone resorption predict hip fractures in elderly women. The EPIDOS Prospective Study. J Bone Miner Res 1996;11:1531-8.
17. Meier C, Nguyen TV, Center JR, Seibel MJ, Eisman JA. Bone resorption and osteoporotic fractures in elderly men: the Dubbo osteoporosis epidemiology study. J Bone Miner Res 2005;20:579-87.
18. Delmas P, Licata A, Reginster J, et al. Fracture risk reduction during treatment with teriparatide is independent of pretreatment bone turnover. Bone 2006;39:237-43.
19. Seibel MJ, Naganathan V, Barton I, Grauer A. Relationship between pretreatment bone resorption and vertebral fracture incidence in postmenopausal osteoporotic women treated with risedronate. J Bone Miner Res 2004;19:323-9.
20. Bauer DC, Garnero P, Hochberg MC, et al. for the Fracture Intervention Research Group. Pretreatment levels of bone turnover and the antifracture efficacy of alendronate: the fracture intervention trial. J Bone Miner Res 2006;21:292-9.
21. Sarkar S, Reginster JY, 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.
22. Reginster JY, 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.
23. Bjarnason NH, Sarkar S, Duong T, Mitlak B, Delmas P, Christiansen C. Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. Osteoporos Int 2001;12:922-30.
24. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas P. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res 2003;18:1051-6.
25. Bauer DC, Black DM, Garnero P, et al. Fracture Intervention Trial Study Group. 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.
26. Chapurlat RD, Cummings SR. Does follow-up of osteoporotic women treated with antiresorptive therapies improve effectiveness? Osteoporos Int 2002;13:738-44.
27. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab 2004;89:1117-23.
28. Delmas PD, Vrijens B, Roux C, et al. A reinforcement message based on bone turnover marker response influences long-term persistence with risedronate in osteoporosis: The IMPACT Study. J Bone Miner Res 2003;18:S374.
29. Chen P, Satterwhite JH, Licata AA, et al. Early Changes in Biochemical Markers of Bone Formation Predict BMD Response to Teriparatide in Postmenopausal Women With Osteoporosis. J Bone Miner Res 2005;20:962-70.
30. Dobnig H, Sipos A, Jiang Y, et al. Early changes in biochemical markers of bone formation correlate with improvements in bone structure during teriparatide therapy. J Clin Endocrinol Metab 2005;90:3970-7.
31. Eastell R, Krege JH, Chen P, Glass EV, Reginster JY. Development of an algorithm for using PINP to monitor treatment of patients with teriparatide. Curr Med Res Opin 2006;22:61-6.