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Symposium on 'Diet and bone health'

Biomarkers of bone health and osteoporosis risk*

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The assay features of biochemical markers of bone turnover have markedly improved in the past few years. The most sensitive and specific markers of bone formation include serum bone alkaline phosphatase, total osteocalcin (including the intact molecule and the large N-mid fragment) and the procollagen type I N-terminal propeptide assay. Among the various markers of bone resorption, measurements of the urinary excretion of N- and C-terminal cross-linked telopeptides) and of serum C-terminal cross-linked telopeptides are the most sensitive and specific. Markers of bone turnover can be used to predict the rate of bone loss in post-menopausal women and can also be used to assess the risk of fractures. In osteoporosis-treatment studies (with alendronate, risedronate, raloxifene) markers of bone turnover appear even more strongly associated with fracture risk reduction than bone mineral density (BMD). These observations support the use of markers of bone turnover as surrogates for fracture risk reduction, perhaps even more so than BMD. Bone markers can also be used to monitor the efficacy of antiresorptive therapy such as hormone-replacement therapy, raloxifene and bisphosphonates in individual patients. Furthermore, they have also proved to be helpful in monitoring the response to nutritional interventions and have the advantage over BMD in that they provide information about mechanism of effect and changes are often observed much more rapidly.

Bone turnover markers: Bone mineral density: Bone health: Osteoporosis

Osteoporotic fractures have a considerable impact on the individual and on health economics. There is a substantial increase in mortality and morbidity, particularly after a hip fracture; 10–20% more women die subsequent to a hip fracture than would be expected for their age, and for those who survive ≤50% cease to be able to live independently[1]. In health economic terms it is estimated that there are >160 000 osteoporotic fractures per year in the UK alone, which cost the National Health Service £$1{\cdot}7 \times 10^9$. Antiresorptive therapies are now available that have been shown to rapidly reduce fracture incidence even in elderly women[2–5]. However, in developing a fracture prevention strategy it is important to be able to identify those women at greatest risk of a fracture.

It is now well established that fracture risk is higher in women with low bone mineral density (BMD), with a decrease of 1 SD in BMD leading to a doubling of the risk of fracture[6]. However, there are numerous other risk factors for osteoporotic fractures and a WHO working party has been developing an approach for the estimation of 10-year fracture risk based on these factors[7]. Recently, attention has turned to the role of biochemical markers of bone turnover as predictors of fracture. Bone turnover may predict fracture in two ways: (a) via BMD, since high bone turnover is associated with low BMD[8]; (b) independently of BMD, since increased bone turnover has a detrimental effect on bone microarchitecture and fragility[9].

Abbreviations: BMD, bone mineral density; CTX, C-terminal cross-linked telopeptides; NTX, N-terminal cross-linked telopeptides; PICP, procollagen type I C-terminal propeptide; PINP, procollagen type I N-terminal propeptide.

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Table 1. Most-commonly-used biochemical markers of bone turnover

Bone formation	Bone resorption
Byproducts of collagen synthesis	Collagen degradation products
Procollagen type I C-terminal propeptide[s]	Hydroxyproline[u]
Procollagen type I N-terminal propeptide[s]	Pyridinoline[u,s]
Matrix protein	Deoxypyridinoline[u,s]
Osteocalcin[s]	Cross-linked telopeptides of type I collagen
Osteoblast enzyme	N-terminal cross-linked telopeptide[u,s]
Total alkaline phosphatase[s]	C-terminal cross-linked telopeptide[u,s]
Bone alkaline phosphatase[s]	C-terminal cross-linked telopeptide generated by matrix metalloproteinases[s]
	Osteoclast enzymes
	Tartrate-resistant acid phosphatase[s]
	Cathepsin K[s]

[s]Measured in serum; [u]measured in urine.

The present review will examine the evidence for the use of biochemical markers of bone turnover in the prediction of osteoporotic fractures.

Biochemical markers of bone turnover

Bone turnover can be easily measured, often with auto-analysers, using a variety of biochemical markers in either serum or urine. Biochemical markers of bone turnover are broadly divided into two categories: markers of bone resorption, which reflect osteoclast activity and are for the most part degradation products of type I collagen; markers of bone formation, which reflect osteoblast activity and are byproducts of collagen synthesis, matrix proteins or osteoblastic enzymes (Table 1). Bone resorption and bone formation are coupled processes and therefore in most situations any of these markers will reflect a change in bone turnover.

Menopause

Oestrogen deficiency caused by ovariectomy or drug therapy, such as gonadotropin-releasing hormone-agonist therapy, results in a rapid increase in the levels of markers of bone turnover[10]. Similarly, the menopause is marked by an increase in levels of markers. The magnitude of the increase varies for the different markers, probably reflecting their specificity for bone or differences in their metabolism in low and high turnover states. The markers probably start to increase in the peri-menopausal period before menstruation has ceased. Premenopausal women aged >40 years have higher levels of C-terminal cross-linked telopeptides (CTX) and osteocalcin than younger women[8], which may be weakly associated with lower BMD. In women with altered menstrual patterns, in whom follicle-stimulating hormone is elevated but oestradiol is still at premenopausal levels, N-terminal cross-linked telopeptides (NTX) are increased by 20% but formation markers are unchanged compared with premenopausal levels[11]. It has recently been shown that the changes in bone turnover in premenopausal and peri-menopausal women may be regulated by inhibins, particulary inhibin A, independently of follicle-stimulating hormone and oestrogen levels[12]. Once the oestradiol levels decrease, markers of bone resorption and formation increase[13].

In the first years of the menopause mean levels of pyridinium cross-links excretion increase and may even be doubled[14–16], but there is still considerable overlap with levels in premenopausal women. The increases in the telopeptides or total cross-links are greater than the increase in the free pyridinolines, possibly for reasons discussed earlier[11,17]. Increases of 80–100% have been found in total cross-links measured by HPLC, 100–130% in telopeptides and 50% in free deoxypyridinoline in a comparative study of fourteen premenopausal women aged 33–44 years and twenty-nine post-menopausal women aged 46–53 years who were within 3 years of the menopause[18]. A considerably smaller increase was found in the serum markers of bone resorption, tartrate-resistant acid phosphatase and CTX generated by matrix metalloproteinases, of the order of 20–25%[19]. Interestingly, cathepsin K appears to be lower in older women compared with premenopausal women[20].

The differences in the increases in markers of bone formation in post-menopausal women may be related to the different aspects of bone formation that each marker reflects. It may also reflect a difference in tissue specificities of the markers. The increases in bone alkaline phosphatase and osteocalcin are of the order of 50–100%, but may be as high as 150%. The increase in procollagen type I C-terminal propeptide (PICP) is considerably less, approximately 20%. Procollagen type I N-terminal propeptide (PINP), which may be the more bone-specific propeptide, shows a greater increase at the menopause[21].

Whether the increase in bone turnover that occurs at the menopause is maintained into old age has been questioned[22], but elevated levels of bone turnover have been found in women into their eighth decade[23]. It has been shown that NTX and CTX and markers of bone formation remain elevated in women for 40 years after the menopause[24].

Osteoporosis

Markers of bone resorption are significantly elevated in post-menopausal women with osteoporosis as compared with normal post-menopausal women, but the markers of

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bone formation are much less elevated and may indeed be decreased[25,26]. This pattern of changes suggests that an extent of imbalance of bone resorption and bone formation occurs in osteoporosis. A mean increase of 40% has been found in the level of total deoxypyridinoline in a group of sixty-three women with post-menopausal osteoporosis compared with a group of sixty-seven normal post-menopausal women[27]. However, there was a considerable overlap of individual levels in the two groups. The heterogeneity of bone resorption in the group with osteoporosis probably indicates different causes of the disease or may represent differences in the stage observed in the individuals in the study. Single measurements of total and free cross-links are unlikely to be useful in identifying osteoporosis in an individual post-menopausal woman. However, a recent study suggests that NTX can discriminate between normal post-menopausal women, women with osteopenia and women with osteoporosis, as defined by the WHO criteria[28]. Recently, it has been shown that the new marker of resorption, cathepsin K, is significantly increased in postmenopausal women with osteoporosis compared with healthy women (11·3 mmol/l *v.* 3·1 nmol/l)[29].

Response to therapy

Currently, bishosphonates are the treatment of choice in post-menopausal osteoporosis. Bisphosphonates are anti-resorptive agents that suppress osteoclast activity. Markers of bone resorption decrease rapidly in response to treatment. Typically, there is a decrease of 50–70% in the telopeptides within the first 12 weeks of treatment[30,31]. It has been shown that there is a significant decrease in urinary NTX within the first 8 weeks of treatment with alendronate. The changes in other markers of bone resorption are somewhat smaller. Serum levels of tartrate-resistant acid phosphatase 5b are reduced by approximately 20%[32]. The markers of bone formation are also significantly reduced in response to bisphosphonates; PINP is reduced by $\leq 60\%$ and bone alkaline phosphatase more modestly by about 40%[30]. Although the efficacy of alendronate and risedronate in reducing fractures is similar, the decrease in bone turnover appears to be greater in patients treated with alendronate.

Treatment with selective oestrogen-receptor modulators such as raloxifene have a smaller effect on markers of bone turnover than bisphosphonates. Serum CTX decreases by 30–40% and tartrate-resistant acid phosphatase 5b by only 10%. The response of the markers of bone formation is also smaller; PINP decreases by 30% and bone alkaline phosphatase by 15–20%[33,34].

In contrast to the antiresorptive drugs, which suppress bone turnover, the new anabolic treatment for osteoporosis, teriparatide, stimulates bone turnover, which combined with a positive remodelling balance leads to an increase in bone mass[35]. Both bone formation and bone resorption markers are increased in response to teriparatide[36]. The procollagen propetides peak 6 months after initiation of treatment (PINP is increased by 200%[37] and PICP by 60%[38]), after which they return towards pretreatment levels. Bone alkaline phosphatase remains elevated throughout treatment, as do markers of bone resorption such as urinary NTX, which may be elevated by 200% after 12 months of treatment[38].

Strontium ranelate has yet another mode of action, which is not understood. It results in small increases in bone formation and a small decrease in bone resorption. However, the changes in bone-turnover markers in response to sodium ranelate are smaller than those seen in response to other treatments; serum CTX decreases by 12% and bone alkaline phosphatase increases by 8%[39].

Prediction of bone loss, fracture and response to therapy

Bone loss

BMD in the post-menopausal woman is determined by peak bone mass and the amount of bone lost since the menopause. With increasing age the contribution of bone loss to the resultant BMD becomes more substantial[40]. Furthemore, increased bone turnover becomes an increasingly important determinant of BMD as women grow older[25]. In several studies bone loss has been shown to correlate with markers of bone turnover, although this finding is not universal. It has been shown that in women in the early years after the menopause there is an inverse relationship between markers of bone turnover and bone loss[41]. In other studies of women in the first 7 years after the menopause a combination of resorption and formation markers or a combination of pyridinoline with oestradiol glucuronide and BMI can predict $\leq 59\%$ of the variance of bone loss at the forearm[42,43]. Change in BMD at the spine and hip, the clinically-relevant sites, can only be poorly predicted, if at all[44–46]. At the forearm high levels of PINP, osteocalcin, urinary NTX and serum CTX are associated with rapid bone loss[47]. In women aged >70 years the correlation between baseline levels of biochemical markers and the annual rate of change in BMD over a 3-year period at the total hip was found to be at best moderate[45]. Although most of these studies indicate that there is a relationship between high levels of bone-turnover markers and increased bone loss they are not sufficiently sensitive to be used to predict bone loss in an individual post-menopausal woman.

Fracture

While biochemical markers of bone turnover may be able to predict bone loss and hence fracture risk, they may also predict fracture risk independently of BMD. High bone turnover *per se* can disrupt the trabecular architecture by increasing the incidence of trabecular perforation and buckling, thus reducing bone strength, without necessarily affecting BMD substantially. In retrospective and prospective studies fracture risk may be associated with increased levels of markers of bone resorption but not bone formation[48,49]. In a short prospective study of elderly French women a 1 SD increase in CTX and free deoxypyridinoline, adjusted for femoral-neck BMD and gait, above the upper limit for premenopausal women was found

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to result in a 2-fold and 1·7-fold increase respectively in risk of hip fracture over a 22-month follow-up period[50]. Increased pyridinolines have also been shown to predict a history of fracture independent of BMD, age and other markers of bone turnover[51]. An association with fracture has also been observed using the two isomers of CTX (α and β); a greater ratio is associated with fracture in French women[52].

However, there is little convincing evidence to indicate that a single measurement of a biochemical marker of bone turnover can predict fracture risk in an individual woman even over a short period of time. The combination of a biochemical marker and BMD may be a much more powerful predictor of fracture than BMD alone[53]. Women with a low hip BMD (<2·5 SD below the premenopausal mean) and high CTX (>2 SD above the premenopausal mean) have a considerably higher risk of hip fracture than those who have only one of these independent risk factors[54].

Biochemical markers of bone turnover cannot substitute for serial BMD measurements, but may be useful when considered in conjunction with BMD measurement.

Response to therapy

Early changes in bone-turnover markers in response to treatment may be predictive of change in BMD and fracture risk. A number of studies have shown that change in CTX and NTX after 6 months predicts change in lumbar-spine BMD at 2·5–4 years later in elderly women treated with alendronate and in hip BMD in elderly women treated with alendronate or hormone-replacement therapy[55,56]. Similar results have been reported in the Danish cohort of the Early Post-menopausal Intervention Cohort Study for younger post-menopausal women treated with alendronate for the prevention of osteoporosis[57].

It has been shown that increases in PICP at 1 month and PINP at 3 months are predictive of change in lumbar-spine BMD at 18 months in women with osteoporosis treated with teriparatide[36]. In addition, baseline levels of markers are also weakly predictive of response to treatment. Similar findings have recently been published[58].

In addition to predicting change in BMD, early changes in bone-turnover markers may predict change in fracture risk. It has been shown that the magnitude of changes in urinary NTX and CTX 3–6 months after the start of risedronate treatment is related to the decrease in vertebral fractures in women with at least one previous vertebral deformity[59]. In the Multiple Outcomes of Raloxifene Evaluation Trial, a randomised placebo-controlled trial of 7705 women with osteoporosis treated with raloxifene for 3 years, change in serum osteocalcin was shown to be predictive of change in vertebral fracture risk and a better predictor than change in femoral-neck BMD in the women treated with raloxifene[54].

Conclusion

Biochemical markers of bone turnover have proved to be useful, non-invasive and relatively inexpensive tools for studying bone metabolism in population studies and are gradually becoming established in clinical practice. In the treatment of the individual post-menopausal woman they may be useful as adjuncts to BMD and other diagnostic tests. Their main use, however, is in monitoring response to treatment. The continued development of new markers of bone turnover will increase the knowledge of the pathophysiology of osteoporosis and other metabolic bone diseases, and after further evaluation these new markers may find a place in the clinical care of post-menopausal women.

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