Biochemical markers of bone turnover and osteoporosis management

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Summary

Osteoporosis is defined as a systemic disease characterised by low bone mass and microarchitectural deterioration of bone tissue, both of which are related to abnormalities of bone turnover. Bone mass can be assessed by measuring bone mineral density (BMD) using dual x-ray absorptiometry (DXA), and there is a large body of evidence that low BMD is an important determinant of fracture risk. However, BMD measurement is not the only determinant of fracture risk. Among other determinants, increased bone resorption evaluated by specific biochemical markers has been shown to be associated with increased risk of hip, spine and non-vertebral fractures independently of BMD. The combination of bone mass measurement and assessment of bone turnover by biochemical markers is thus helpful in the assessment of osteoporotic fracture risk. Repeated measurements of biochemical markers during treatment appear to improve the management of osteoporotic patients. The decrease in bone turnover markers during antiresorptive treatment is related to the subsequent increase in BMD. Further, several studies have shown that short-term reductions in bone turnover were associated with a reduction in vertebral and/or non-vertebral fracture risk in women treated with antiresorptive agents.

Introduction

Osteoporosis is defined as a systemic disease characterised by low bone mass and microarchitectural deterioration of bone tissue, both of which are related to abnormalities of bone turnover. Bone mass can be assessed by measuring bone mineral density (BMD) using dual X-ray absorptiometry (DXA), and there is a large body of evidence that low BMD is an important determinant of fracture risk [1–3]. There is a consistent doubling of fracture risk for each SD reduction in BMD, irrespective of fracture type and BMD measurement site. However, there is no threshold below which fracture risk increases, which indicates rather a gradient of risk of fracture with decrease in BMD. The risk prediction has been found across various age ranges, but the gradient of risk decreases in advanced age [1]. But BMD is not the only determinant that contributes to bone strength and fracture risk. Bone fragility is also dependent on morphology, architecture, remodeling of bone and qualitative properties of bone matrix [4, 5]. Much effort has gone into the identification of predictors of osteoporotic fracture risk. In the treatment-naïve patient, age, gender, comorbidity, disability, calcium intake, low body mass index, low bone mass and prevalent fractures are the most common and powerful predictors of osteoporotic fracture [5, 6]. More recently it has become evident that accelerated bone turnover is also associated with a higher risk of osteoporotic fracture, irrespective of age, disability and bone mass.

In recent years considerable progress has been made in isolating and characterising cellular and extracellular components of the skeletal matrix, which in turn has facilitated the development of biochemical markers that specifically reflect either bone formation or bone resorption [7, 8]. These biochemical indices have greatly enriched the spectrum of analytes used in the assessment of skeletal pathologies. They are non-invasive, comparatively inexpensive and, when applied and interpreted correctly, helpful tools in the diagnostic and therapeutic assessment of metabolic bone disease. Biochemical markers of bone turnover can be divided into two groups: markers of resorption and markers of formation (Table 1). The principal, specific markers of bone formation, measured in serum by immunoassays, are bone alkaline phosphatase (BAP), osteocalcin (OC), and the procollagen type I N-terminal propeptides (PINP). Markers of bone resorption are the pyridinium crosslinks (pyridinoline and deoxypyridinoline), their associated peptides (telopeptides), released during collagen breakdown and tartrate resistant acid phosphatase (TRAP). Total pyridinium crosslinks are measured by HPLC, but more recently immunoassays for pyridinoline (PYD) and deoxypyridinoline (DPD) in urine and for C-terminal and N-terminal type I collagen peptides (CTX and NTX respectively) have become available. Immunoassays, which preferentially detect the TRAP isoenzyme 5b, predominantly expressed by osteoclasts, have been newly developed. TRAP5b isoenzyme is thought to represent mainly osteoclast number and activity and not directly the rate of collagen breakdown. Many of these assays have been adapted to an automated platform with increased precision and accuracy, making for more widespread availability of these markers.

Biochemical markers and the rate of bone loss

There is evidence that bone turnover increases rapidly after the menopause, and this increase in bone turnover persists long, up to 40 years, after the menopause [9, 10]. In general bone loss at the spine in the immediate menopausal period is approximately

Table 1
Biochemical markers of bone turnover.

Bone formation	Bone resorption
Bone alkaline phosphatase (BAP)	Pyridinium crosslinks
Osteocalcin (OC)	Pyridinoline (PYD)
Type I collagen extension propeptides (PICP, PINP)	Deoxypyridinoline (DPD)
	Crosslinking telopeptides of type I collagen C-terminal (CTX) – N-terminal (NTX)
	Tartrate resistant acid phosphatase (TRAP)
	Galactosyl-hydroxylysine
	Hydroxyproline

1% per year, but as many as one-third of postmenopausal women lose bone at a rate exceeding 1% per year. Cross-sectional data suggest that a sustained increase in bone turnover is associated with faster and greater bone loss. It has been more difficult to assess this relationship in longitudinal studies, as the amount of bone loss is in the same order of magnitude as the precision error of BMD measurement [11, 12]. A strong correlation between the rate of turnover and rate of bone loss has been demonstrated only in a study measuring BMD at a precise site, i.e. the radius, but not with measurements at the spine and hip [11, 13]. However, there is some evidence that biochemical markers can detect "rapid losers" and predict women most likely to respond to antiresorptive therapy, i.e. hormone replacement therapy [14–16].

Increased bone turnover, assessed by biochemical markers, is associated with increased fracture risk.

At the present time a single measurement of a biochemical marker cannot predict the absolute rate of bone loss in a single individual. However, increased bone turnover markers can be regarded as a risk factor for rapid bone loss.

Biochemical markers and fracture risk

As mentioned above, there is a strong association between BMD and the risk of hip, spine and forearm fractures. However, up to half of patients with incident fractures have baseline BMD, assessed by dual X-ray absorptiometry (DXA), above the diagnostic threshold of osteoporosis defined as a T-score of -2.5 SD or more below the average value for young healthy women [17–19]. There is thus a need for improvement in the identification of patients at risk for fracture. Furthermore there is increasing evidence that the decision to use pharmacological intervention for prevention of fracture should be based on the fracture probability rather than only on the presence of osteoporosis as defined by BMD [5, 6]. A potential clinical application for biochemical indices of skeletal metabolism is in the assessment of fracture risk. Findings of prospective studies indicate an association between osteoporotic fracture and indices of bone turnover, irrespective of bone mineral density in women at the menopause and in elderly women, and more recently also for men [20–26].

The results for the relationship between bone formation markers and fracture risk are conflicting. In the French cohort study of elderly women (EPIDOS) no significant relationship between OC and BAP could be demonstrated over a 2–year follow-up, whereas in younger healthy postmenopausal women (OFELY and HOS) a significant association between increased BAP serum levels and risk of vertebral as well as non-vertebral fracture was found [20–22]. In the OFELY study a reassessment was performed after a median 10–year follow-up and a significant positive association between baseline serum levels of OC, BAP and PINP and the risk of fracture was found [19, 27]. In contrast others did not find a significant relationship between a bone formation marker and fracture which occurred within the following 20 years [28].

More concordant results were obtained with markers of bone resorption. In five prospective studies (EPIDOS, Rotterdam, OFELY, HOS, and Malmö) a significant relationship between baseline levels of urinary or serum CTX, urinary free DPD, or serum TRAP5b and fracture risk could be demonstrated [9, 20–24] (figure 1 and table 2). An increase in these markers above the premenopausal range was associated after adjustment for BMD with a twofold increase in risk for hip, vertebral and non-vertebral fractures, over a follow-up period of 1.8 to 5 years. These results suggest

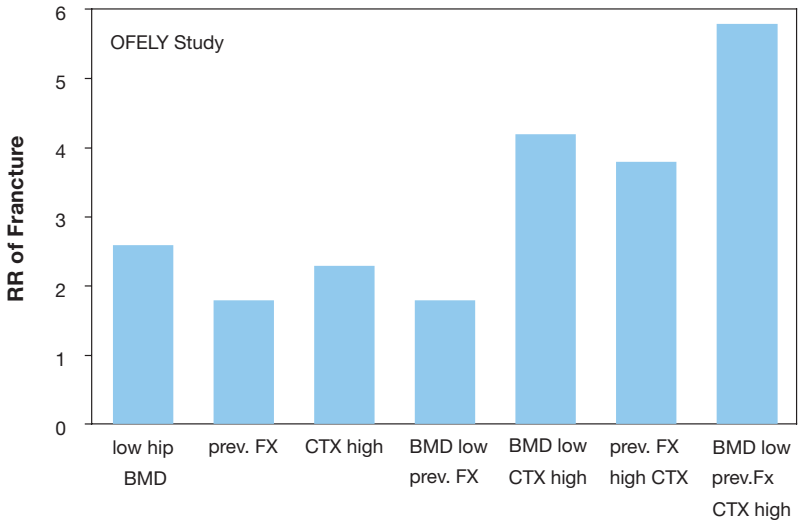

Figure 1. Combination of different independent predictors to identify women with the highest risk of fracture. BMD: bone mineral density, CTX: c-terminal telopeptide, Fx: fracture (from Ref. (21)).

Table 2
Relationship between increased bone resorption rate and fracture risk. (Fx: fracture, BMD: bone mineral density, CTx: c-terminal telopeptide, fDPD: free deoxypyridinoline, TRAP: tartrate resistant acid phosphatase, u: urinary, s: serum)

Study	Age (years)	Fx	RR-BMD (95% CI)	Marker	RR-Marker (95% CI)
EPIDOS	>75	hip	2.8 (1.6–5.1)	u-CTx	2.2 (1.3–3.6)
				fDPD	1.9 (1.1–3.2)
OFELY	64 (mean)	all	2.8 (1.4–5.6)	u-CTx	2.3 (1.3–4.1)
				s-CTx	2.1 (1.1–3.6)
HOS	69 (mean)	all	1.6 (1.2–2.2)	u-CTx	1.6 (1.2–2.0)
Rotterdam	>75	all	1.3 (0.6–2.7)	u-DPD	1.9 (1.2–3.8)
Malmö	>75	all	2.2 (1.5–3.1)	TRAP	2.2 (1.2–4.2)

that a combined approach, with BMD and indices of bone turnover, could improve fracture prediction in postmenopausal women. In fact, calculating the absolute risk such as 10–year probability of fracture based on 2 prospective studies (EPIDOS and OFELY), it was found that combining clinical risk factors (i.e. previous fracture), BMD and bone turnover, gives a 10–year probability of hip fracture some 70–100% higher than that associated with low BMD alone [29] (figure 2). Thus there is evidence that patients with low bone mineral density and high bone turnover are at high risk for osteoporotic fractures.

Biochemical markers and monitoring treatment

Another domain for the clinical use of biochemical bone markers is monitoring of osteoporosis therapy. This application includes monitoring both therapeutic efficacy (i.e. prediction of therapeutic response in regard to changes in BMD and reduction in fracture risk) and patient compliance. The ultimate goal in treating patients with osteoporosis is to reduce the fracture risk. However, the short-term incidence of osteoporotic fractures is low, and absence of fracture during treatment does not necessarily mean that the treatment is effective. Thus, monitoring the effect of treatment by fracture incidence alone would be inadequate for most practical purposes. Consequently, serial measurements of changes in BMD as a surrogate marker of therapeutic efficacy are currently the standard approach in monitoring osteoporosis therapy. However, changes in BMD occur slowly and therapeutic effects are usually not detectable for several years of treatment [16, 30–33]. In contrast, biochemical markers of bone turnover change much faster than BMD in response to therapeutic interventions [16]. In several prospective intervention trials with antiresorptive agents it has been shown that a rapid decrease in bone resorption markers occurs after as little as 2–4 weeks and reaches a plateau after 3–6 months [16, 34]. The decrease in bone formation markers, reflecting the physiological coupling of bone formation to bone resorption, is delayed and reaches a plateau after 6–12 months. The magnitude of the decreases varies according to the antiresorptive potency of the medication. On bisphosphonate treatment urinary CTX and NTX decrease by about 40–70% and total DPD by about 50% [34, 35]. Compared with bisphosphonates, raloxifene induces smaller decreases in bone resorption markers, of about 30–40% for urinary CTX and 20–30% for bone formation markers [36]. Calcium and vitamin D supplements induce small but significant decreases in bone resorption markers, of about 10–20% [37]. The decrease in bone turnover markers during antiresorptive treatment is inversely related to the subsequent increase in BMD, predominantly at the lumbar spine [38]. Several studies in postmenopausal women treated with antiresorptive

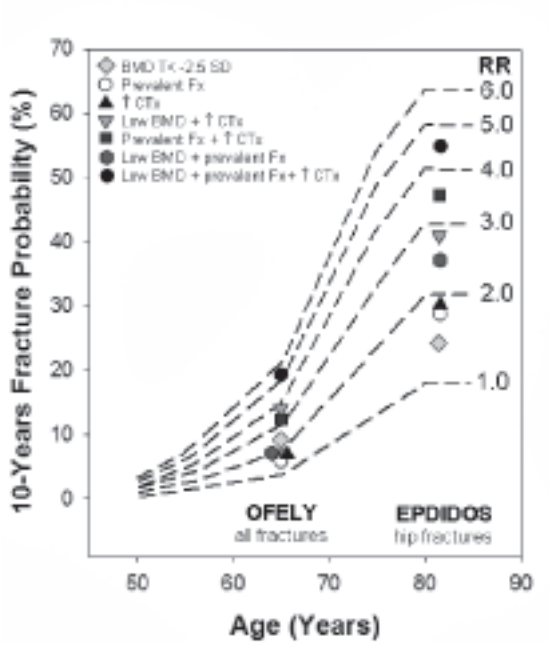

Figure 2. Combination of clinical risk factors, bone mineral density and bone turnover measurements to identify women with the highest risk of fracture. The figure shows the ten-year probability of hip fracture according to age and relative risk. The symbols show the effect of risk factors on fracture probability derived from women aged 65 years (OFELY study) and 80 years (EPIDOS study). The data from the OFELY study are derived from information on all fractures. Low hip BMD was defined as values at 2.5 SD or below the mean of young adults. High urinary CTX corresponds to values above the upper limit of premenopausal women (mean+2SD) (from Ref. [29]).

agents (HRT, raloxifene, bisphosphonates) have indicated that the degree of short-term reduction in bone turnover markers (after 3–6 months) correlates with the observed long-term increase in BMD after 1–3 years of treatment [14, 34,38–42].

Changes in bone turnover markers on treatment are related to the increase in BMD and decrease in fracture risk.

Although several randomised trials have found that antiresorptive agents improve BMD and reduce the risk of fractures, recent studies have provided evidence that the observed reduction in fracture risk is only partly explained by the documented changes in BMD. The reduction in risk was greater than predicted from improvements in BMD, and it has been estimated that change in BMD explains only 4–28% of the reduction in vertebral fracture risk attributed to antiresorptive treatment [30, 43–47]. It is therefore possible that changes in other determinants of bone strength, including the rate of bone turnover and its changes during antiresorptive therapy, may be more predictive of anti-fracture efficacy than changes in BMD. In fact, several studies have confirmed that short-term reductions in bone turnover were associated with a reduction in vertebral and/or non-vertebral fracture risk in women treated with HRT, raloxifene, risedronate, and alendronate [26, 35, 44, 48, 49]. Recent published studies have investigated the change in bone turnover markers and fracture risk in bisphosphonate-treated postmenopausal women. It was found that reductions in urinary C-terminal telopeptides (CTX) by 60% and N-terminal telopeptides (NTX) by 51% on 3–6 months of risedronate treatment were significantly associated with the reduction in vertebral and non-vertebral fracture risk after 3 years [35]. The change in bone resorption markers accounted for more than 50% of the risedronate-related fracture risk reduction for both vertebral and non-vertebral fractures. Interestingly, there appears to be a threshold level for the decrease in bone resorption markers (e.g. 55–60% as measured by CTX, and 35–40% as measured by NTX) below which there was no further increase in therapeutic benefit.

Potent bone formation stimulating therapy with peptides from the parathyroid hormone family has recently become available [50, 51]. In contrast to antiresorptive agents, PTH administered intermittently in low doses increases bone remodelling, stimulating bone formation preferentially over bone resorption and thus resulting in net gain of bone. Teriparatide (PTH 1–34) and PTH (the full-length peptide, PTH 1–84) have been shown to increase bone mineral density (BMD). Teriparatide reduces spine and non-vertebral fractures, an effect that is sustained for up to 30 months after the withdrawal of treatment. The intact hormone (1–84 amino acids) showed similar results on spine fractures. Increases in bone turnover markers indicate a skeletal response to PTH and there is evidence that early measurement of bone formation markers (OC, BAP and particularly PINP) correlates positively with the subsequent BMD response [52–55]. These data suggest that serial bone marker measurements could become useful in identifying skeletal responders to anabolic therapy with PTH.

Long-term adherence and persistence with any therapy is very poor and is not specific to the disease, disease severity, or treatment. As with other diseases, poor compliance and persistence is a concern in osteoporosis due to its negative impact on fracture risk and healthcare costs [56]. Adherence to bisphosphonate therapy is associated with significantly greater fracture risk reduction [56]. However, the probability of continuing treatment with a bisphosphonate after 1 year is only 50% [57]. Published data suggest that monitoring visits during antiresorptive drug treatment may enhance adherence and there is preliminary evidence that monitoring with a bone turnover marker during antiresorptive therapy may also improve adherence [58–60]. In a post-hoc analysis, patients monitored with bone turnover markers and a nurse visit, and given a positive message regarding their response to antiresorptive therapy, were 92% more likely to adhere to therapy compared with usual care, and 18% more likely to adhere to therapy than patients monitored with a nurse visit alone [58]. The type of message patients were given from the bone resorption marker results impacted their subsequent persistence with therapy, a positive message being associated with improved persistence while a neutral message had no effect and a negative message reduced persistence [58, 60]. Monitoring anti-osteoporotic treatment using bone markers may thus be useful in improving persistence with treatment and thus its effectiveness.

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