The Value of Biochemical Markers of Bone Turnover in Osteoporosis

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ABSTRACT. A number of biochemical markers of bone turnover have been described and these reflect the activity of osteoblasts (bone formation) or osteoclasts (bone resorption). These markers have the following advantages for the measurement of bone turnover: (1) they are noninvasive; (2) inexpensive; (3) can be repeated on many occasions; (4) and reflect bone cell activity in the entire skeleton. They have disadvantages: (1) they do not provide information about the work of individual cells; (2) they do not reflect the process of mineralization; and (3) their levels may be affected by the rate of clearance. The markers have been used to study the pathogenesis of osteoporosis, identify postmenopausal women with accelerated bone loss, predict fracture independently of bone loss, predict response to therapy, and monitor response to therapy. They may also be useful in the setting of clinical trials for choosing minimal and maximal effective doses, understanding the mechanism of the changes in bone mineral density (BMD) and studying the effect and time course of changes in bone after cessation of therapy. Markers do not provide a surrogate for fracture risk or BMD. However, they do have uses in osteoporosis and can provide preliminary data in the short term that can be used in the design of longterm studies of BMD and fracture. (*J Rheumatol 1997;24:1215–7*)

Key Indexing Terms:
OSTEOPOROSIS OSTEOCALCIN ALKALINE PHOSPHATASE
COLLAGEN PYRIDINIUM CROSSLINKS HYDROXYPROLINE

Bone turnover may be evaluated by bone histomorphometry, combined calcium balance and kinetic studies, and biochemical markers of bone turnover. Biochemical markers have the advantages that they are noninvasive, inexpensive, reflect turnover in the whole skeleton, and allow repeated evaluation. They have the disadvantages that they do not provide information about the work of individual cells, they do not reflect mineralization, and they are subject to clearance effects. For example, during pregnancy osteocalcin levels are low, not because bone turnover is low, but because osteocalcin is cleared by the placenta[1].

A number of biochemical markers are available for the evaluation of bone turnover, reflecting the activity of osteoblasts (bone formation) or osteoclasts (bone resorption). These are shown in Table 1.

CLINICAL APPLICATION OF BIOCHEMICAL MARKERS IN OSTEOPOROSIS

Markers of bone turnover in established osteoporosis. Almost all studies have shown that bone resorption is somewhat higher in patients with overt osteoporosis, although there is considerable overlap with age matched controls[18,19]. Levels of biochemical markers of bone formation are also usually found to be higher in patients with overt osteoporosis[19]. Markers of bone turnover are poorly predictive of bone mineral density (BMD), and cannot be used to diagnose osteoporosis or to select patients for subsequent densitometry.

A number of factors may explain the limited discrimination of markers of bone turnover for osteoporosis, including heterogeneity of the osteoporotic syndrome, the possible confounding effect of recent fracture on markers, and the fact that the mean increase in bone turnover is small in comparison with the biological variability of markers of bone turnover.

The finding that both bone resorption and bone formation may be increased in postmenopausal osteoporosis raises the issue of how these 2 processes could be compared. This

Table 1. Biochemical markers of bone turnover. All markers of bone formation are measured in the serum. All markers of bone resorption are measured in the urine, except for tartrate resistant acid phosphatase. Assays are currently under development for more serum based measurements of bone resorption. Pyridinium crosslinks of collagen may be measured by high performance liquid chromatography (free and total) or by immunoassay (free)[12]. Fragments of type I collagen from the region of the crosslinks can also be measured from the N-telopeptide[13] and C-telopeptide regions by immunoassay (in urine[14] and serum[15]).

Bone Formation	Bone Resorption
C-and N-propeptides of type I collagen[2–4]	Hydroxyproline[9]
Osteocalcin[5]	Hydroxylysine glycoside[10]
Bone isoform of alkaline phosphatase[6–8]	Pyridinium crosslinks of collagen and related collagen fragments (telopeptides)[9–11]
	Tartrate resistant acid phosphatase[16,17]

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could be addressed by comparing the percentage increase in either marker, but this approach may give misleading results if the marker is not specific for bone, or if the reference range for one marker is wider than for another.

The use of markers to predict postmenopausal bone loss. High rates of bone turnover may be associated with an increased rate of bone loss in women after menopause. It is therefore possible that biochemical markers of bone turnover could be useful as part of a public health strategy to identify subjects at risk of future osteoporosis. Ultimately, if these measurements are to be useful in a screening context, they have to be predictive of longterm (> 10 years) bone loss at relevant skeletal sites (spine and hip) in individual subjects[20].

There is some evidence that biochemical measurements can predict the rate of bone loss at some skeletal sites in women very soon after menopause[21], although several recent preliminary studies have failed to show any such relationship using a variety of markers of bone turnover in either early postmenopausal women or in older women[22,23]. One study[24] showed a significant relationship only at the total hip, but not at other skeletal sites. It appears that there is more variability in rates of bone loss from the forearm than from the spine[25]. This may explain why markers may relate to bone loss at one site, but not at another.

Prediction and monitoring of response to therapy. Treatment of postmenopausal osteoporosis with antiresorptive agents such as estrogen or bisphosphonates reduces bone turnover. In general, the onset of the decrease in markers of bone formation is gradual, and levels continue to decrease for at least 6 months (Figure 1). In contrast, markers of bone resorption tend to decrease rapidly, and reach steady state within 6 months[26]. The timing of sample collection relative to the onset of therapy is therefore critical to the interpretation of any measurement. On a population basis, biochemical markers of bone turnover before therapy may be useful to predict the response to therapy[27], markers and can also be used to show that bone resorption is decreased in response to therapy. For example, the change in biochemical markers at 3 months may predict the change in BMD at 2 years[28–30]. However, the clinical utility of these measurements to decide whether an individual patient should receive therapy, or to adjust the dose of antiresorptive agents during therapy, is uncertain. It is necessary to determine whether the change in bone turnover is predictive of longterm changes in BMD in individual subjects.

There is insufficient data at present to recommend use of biochemical markers in a screening context to predict the risk of osteoporosis in individual subjects, or to monitor therapy in routine clinical practice.

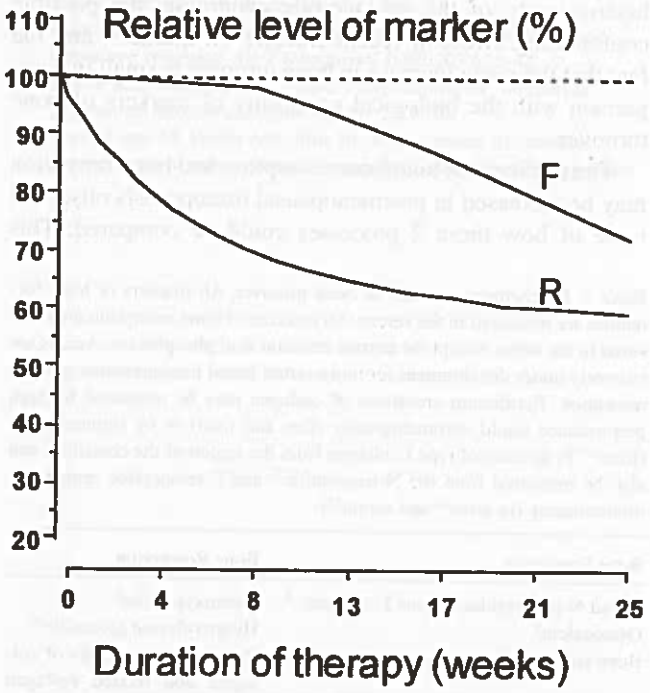

Figure 1. Time course of response to hormone replacement therapy or bisphosphonate therapy for markers of bone formation (F) and markers of bone resorption (R).

BIOCHEMICAL MARKERS IN THE SETTING OF CLINICAL TRIALS

Markers may be useful in establishing dose–response relationships between antiresorptive therapy and bone resorption. This has been evaluated in the short term (6 weeks)[30] and in the longterm (2 years)[31] in studies of the bisphosphonate, alendronate. Markers may be helpful in understanding the mechanism underlying the changes in BMD. For example, the bone resorption marker deoxypyridinoline decreases by 50% by 6 months of alendronate treatment (10 mg/day)[26,31] and yet BMD of the spine continues to increase for 2 to 3 years. This cannot simply be due to the filling in of remodeling space, as the remodeling cycle lasts only 5 months. That bone resorption markers do not decline progressively is reassuring and indicates that bone turnover is not being reduced to levels below which microfractures may accumulate ("deep frozen bone"). Indeed, bone turnover usually returns to the level found in healthy premenopausal women[28].

Information may also be obtained about the effect of stopping treatment. It has been a concern with bisphosphonates that they are stored in bone for many years and may influence bone turnover long after they are stopped. However, after 6 months' treatment with alendronate, the markers have returned to pretreatment levels by 6 months[32]. After one year's treatment the markers have returned to pretreatment levels by 6 to 12 months[31].

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