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P. Garnero

MARKERS OF BONE TURNOVER FOR MONITORING ANTIRESORPTIVE TREATMENT OF OSTEOPOROSIS

INTRODUCTION

Monitoring the efficacy of treatment of osteoporosis is a challenge. The goal of treatment is to reduce the occurrence of fragility fractures. Measurement of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) is a surrogate marker of treatment efficacy that has been widely used in clinical trials. Its use in the monitoring of treatment efficacy in the individual patient, however, has not been validated. Given a short term precision error of 1 to 1.5 % of BMD measurement at the spine and hip, the individual change must be greater than 3 to 5 % to be seen as significant. With bisphosphonates such as alendronate, repeating BMD 2 years after initiating therapy will allow to detect if a patient is responding to therapy, i.e., shows a significant increase in BMD, at least at the lumbar spine which is the most responsive site. With treatments such as raloxifene or nasal calcitonin that induce much smaller increase in BMD, DXA is not appropriate to monitor therapy and with any treatment, DXA does not allow to identify all responders within the first year of therapy. Failure to respond may be due to non compliance, to poor intestinal absorption (i.e., bisphosphonates), or to other unidentified factors.

BIOCHEMICAL MARKERS FOR BONE TURNOVER

Bone remodeling is the result of two opposite activities, the production of new bone matrix by osteoblasts and the destruction of old bone by osteoclasts. The rates of bone production and destruction can be evaluated either by measuring predominantly osteoblastic or osteoclastic enzyme activities of by assaying bone matrix components released in the bloodstream and excreted in the urine. Increasingly specific biochemical markers for bone remodeling have been identified in recent years (review in [1]). At present, the most sensitive markers for bone production are serum osteocalcin, bone alkaline phosphatase, and procollagen type I N-terminal propeptide (PINP). For the evaluation of bone resorption, immunological assays of pyridinium cross-links of collagen have superseded total pyridinoline assay by high performance liquid chromatography (Table 1). Immunological assays are now available for pyridinoline and deoxypyridinoline in urine and for C-terminal and N-terminal type I collagen peptides (CTX and NTX, respectively) in serum or urine. In the near future, advances in our knowledge of bone matrix biochemistry, most notably of post-translation changes in type I collagen, may allow to identify markers for specific bone diseases. Recently, studies have found that racemization and isomerization of the aspartic acid of CTX were remarkedly reduced in Paget's disease [2, 3] but not in osteoporosis. This abnormality can be demonstrated *in vivo* using monoclonal antibodies specific for each collagen type. Additional work is needed to look for other posttranslation changes in collagen.

Table 1: Biochemical markers for bone remodeling (the markers with the best performance characteristics in osteoporosis are in bold type.

Formation

Serum
- **Osteocalcin** (bone Gla-protein
- Total and **bone alkaline phosphatase**
- Collagen type I C-terminal and N-terminal propeptides (PICP and **PINP**)

Resorption

Plasma/serum
- Tartrate-resistant acid phosphatase (TRAP)
- Free pyridinoline and deoxypyridinoline
- N-terminal (NTX) and **C-terminal (CTX) telopeptide of type I collagen**
- Bone sialoprotein (BSP)

Urine
- **Free pyridinoline and deoxypyridinoline**
- **N-terminal (NTX) and C-terminal (CTX) telopeptide of type I collagen**
- Calcium
- Hydroxyproline
- Galactosylhydroxylysine

EFFECTS OF ANTIRESORPTIVE THERAPY ON TURNOVER AND PREDICTION OF BMD CHANGES BY BONE MARKERS UNDER ANTIRESORPTIVE THERAPY

Several randomised placebo-controlled studies found that resorption-inhibiting therapy was associated with a prompt decrease of bone resorption markers that can be seen as early as 2 weeks with a plateau reached within 3 to 6 months. The decrease of bone formation markers is delayed – reflecting the physiological coupling of formation to resorption – and a plateau

is usually achieved within 6 to 12 months. In addition, in these studies the magnitude of the short-term bone marker level decrease was significantly correlated with the magnitude of the long-term bone mineral density increase [4–13]. Although bone markers do not allow to predict bone gain accurately in individual patients, measurement of a marker for resorption and/or formation can provide the same information on therapeutic efficacy as measurement of bone mineral density. Indeed for the clinician, the primary concern is the identification of non-responders, i.e., of patients who will fail to demonstrate a significant increase of BMD after 2 years of treatment. A BMD response has been defined either as a positive BMD change or as a positive change greater than the precision error in a single individual, also called the least significant change. Several methods have been suggested to identify responders/non responders according to the bone marker response to therapy. One approach is to consider the least significant change of a bone marker (based on the short term or long term within subject variability), regardless of the BMD response. The percentage change of the marker under treatment can be used, and cut-off values can be obtained with a pre-specified sensitivity or specificity. Using this strategy several recent studies have shown that bone markers are reliable indices of therapeutic efficacy in individual patients (Table 2) [5, 6, 10–13]. We also recently showed that combining an absolute bone marker value obtained three to six months into therapy with the percentage decrease in the same marker over the same period in a logistic regression model improved the ability of the marker to identify non-responders to alendronate or estrogen replacement therapy [11, 12].

The value of BMD changes to predict the risk of fracture under treatment is debated, especially because some treatments – such as raloxifene – can induce a 30 to 50 % reduction in vertebral fracture rate despite a small 2 to 3 % increase of BMD at all skeletal sites. Thus, BMD changes may not be an adequate surrogate endpoint to analyse the ability of bone markers to predict fracture risk. It was recently reported that the short term changes of serum osteocalcin and bone alkaline phosphatase under raloxifene were associated with the subsequent risk of vertebral fractures in a large subgroup of osteoporotic women enrolled in the MORE study, while changes in BMD were not predictive [14].

In conclusion, long-term treatment of symptom-free patients raises special challenges because the benefits of the treatment are not perceived by the patients. In this situation, an improvement in a laboratory test may allow to convince the patient that the treatment is having beneficial effects. Several studies have shown that the percentage decrease of some bone markers after 3 to 6 months of HRT or alendronate can be used to predict the 2 year response in BMD with adequate sensitivity and specificity. Prospective studies looking for a favourable effect of bone marker monitoring on treatment compliance and ultimately fracture risk reduction are needed.

Table 2: Early changes in bone remodeling markers to predict the efficacy of estrogen replacement therapy with 90 % specificity in individual patients. From Delmas et al. [12].

Marker	Cutoff value for the bone marker decrease after 3 months	Sensitivity*	Likelihood of a positive response**
Serum CTX	–33 %	68 %	87 %
Urinary CTX	–45 %	60 %	88 %

* Proportion of women whose bone marker value decrease three months into therapy was equal to or greater than the cutoff, among the women with a greater than 2.26 % BMD increase two years into therapy

** Proportion of women with a greater than 2.26 % BMD increase two years into therapy, among the women whose bone marker value decrease three months into therapy was equal to or greater than the cutoff

In this study, 569 postmenopausal women aged 40 to 60 years with a time since menopause shorter than six years were given either a placebo or a transdermal estrogen in a dosage of 25, 50, or 75 µg twice a week for 28 days (continuous treatment) or 50, 75, or 100 µg twice a week for 25 days per cycle (cyclic therapy). Bone mineral density (BMD) at the spine was measured at baseline and after two years using dual-energy X-ray absorptiometry (DXA). Women with a BMD increase versus baseline greater than 2.26 % (i.e., twice the short-term coefficient of variation for DXA) were classified as treatment responders and women with a BMD decrease versus baseline of more than 2.26 % as nonresponders. The table shows the sensitivity and the likelihood of a positive response obtained using a three-month bone marker decrease cutoff associated with 90 % specificity.

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Patrick Garnero is the Managing and Scientific Director of Synarc in Lyon, France and Director of Research and Development in Biochemistry of Synarc, Inc. In addition, he is a research scientist at INSERM in Lyon, France. He received his MSc in Biochemistry and Molecular Biology from the University of Marseilles, and his PhD with honors in Biology and Biochemistry in Lyon. He then continued his research training at Hôpital Cantonal in Geneva, Switzerland and at the Centre for Clinical and Basic Research in Copenhagen, Denmark. Dr Garnero's research focuses mainly on the development of new biochemical markers of bone, cartilage and synovium turnover. He also directs quality assurance in biochemical assays for clinical trials and epidemiological studies in osteoporosis.

Dr Garnero is a member of the American Society for Bone and Mineral Research, which awarded him the Young Investigator Award in 1994. He is also a member of the Committee on Standardization of Biochemical Markers of Bone Turnover of the International Federation of Clinical Chemistry. In addition, he has published over 50 articles in international scientific journals and book chapters.

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