Chapter 34. Biochemical Markers of Bone Turnover in Osteoporosis

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INTRODUCTION

Bone metabolism is characterized by two opposite activities coupled at a basic multicellular unit (BMU). During bone resorption, dissolution of bone mineral and catabolism of bone matrix by osteoclasts results in the formation of resorptive cavity and the release of bone matrix components. Then, during bone formation, osteoblasts synthesize bone matrix that fills in the resorption cavity and undergoes mineralization. There are two groups of biochemical bone turnover markers (BTMs). Bone formation is assessed by osteocalcin (OC), bone-specific alkaline phosphatase (BALP) and N- and C-terminal propeptides of type I procollagen (PINP and PICP). Bone resorption is assessed by N- and C-terminal cross-linking telopeptides of type I collagen (NTX-I and CTX-I), C-terminal cross-linking telopeptides of type I collagen generated by metalloproteinase (CTX-MMP, ICTP), deoxypyridinoline (DPD), hydroxylysine glycosides, or isoform 5b of TRACP (TRACP5b).

GENERAL LIMITATIONS OF BTMS AND THEIR ANALYTICAL AND PREANALYTICAL VARIABILITY

The analytical variability (assessed by the interassay and intra-assay coefficients of variation) depends on the BTM and the measurement method. The preanalytical variability has a strong effect on the BTM levels. It comprises a large number of factors (Table 1), which may coexist in one person (e.g., in a patient with rheumatoid arthritis, BTMs depend on the disease, corticotherapy, and limited mobility). Collection of serum should be performed in standardized conditions, preferably in the fasting state in the morning. For urinary collection, the choice between a spot (usually second morning void) and a 24-h collection is a trade-off between the biological interest and practical reliability. The 24-h collection reflects the overall bone metabolism, whereas the spot collection may be performed in a controlled way.

SELECTED DETERMINANTS OF THE PREANALYTICAL VARIABILITY

Circadian rhythm has a strong impact on the variability of BTMs, especially bone resorption markers that peak in the second half of the night and have their nadir in the afternoon. The amplitude is higher for CTX-I than for other BTMs. Food intake has a strong effect on bone resorption. This postprandial decrease in the serum CTX-I is most probably mediated by glucagon-like peptide 2, the synthesis of which is stimulated by food intake.

In the elderly, bone metabolism is strongly influenced by the vitamin D and calcium status. BTM levels are increased mainly in the institutionalized and home-bound vitamin D-deficient elderly who have lower 25-hydroxycholecalciferol [25(OH)D] concentrations and higher PTH concentrations than the ambulatory ones. 25(OH)D is lower and PTH and BTM levels are higher during winter.

BTM levels are increased in patients with bone metastases and ICTP and α-α-CTX-I (nonisomerized form of CTX-I) seem to be the most sensitive markers of bone involvement. Their levels are positively associated with the spread of bone metastases, the progression of the disease, and skeletal-related events. During an antinecancer treatment, poor decrease in the BTM levels predicts the progression of bone disease and death.

BTM levels are influenced by a recent fracture. During the first hours after fracture, OC decreases because of high cortisol secretion (stress). Then, bone formation and resorption increase reflecting the healing of the fracture. The BTM levels are increased mainly for 4 mo after fracture, and then they decrease for up to 1 yr.

Endogenous and exogenous corticosteroids increase the risk of osteoporosis. They inhibit bone formation. The decrease in the OC level is most rapid followed by a delayed and milder decrease in PICP and PINP. Bone resorption can increase; however, data are less consistent. Low-dose prednisone (5 mg/d) decreased bone formation but not bone resorption. Inhaled corticosteroids induce a dose- and drug-dependent decrease in the OC concentration without significant effect on other BTMs. Inhibitors of aromatase (used in the treatment of breast cancer) reduce the residual secretion of estrogens leading to an acceleration of bone turnover and bone loss. This increase is not observed in the case of the concomitant treatment with bisphosphonates or tamoxifen.

CHANGES IN BTM LEVELS AFTER MENOPAUSE

In young adults, quantity of bone formed at every BMU is equal to the quantity of bone removed by resorption. After menopause, BTMs increase rapidly. Bone formation increases to fill in the higher number of resorption cavities, which increases serum levels of bone formation markers. Because the quantity of bone formed is lower than the quantity of bone resorbed, there is a net bone loss at the BMU level. The increased number of BMUs is the principal determinant of the postmenopausal BTM levels and BMD.

ASSOCIATION BETWEEN BTM LEVELS AND RATE OF BONE LOSS

In some studies, baseline BTM levels are correlated with the subsequent bone loss, which suggests that the bone turnover rate determines the subsequent bone loss. However, for a given BTM level, there is a large scatter of individual values of bone loss, and BTM cannot be used for prediction of the accelerated bone loss at the individual level.

ASSOCIATION BETWEEN BONE TURNOVER RATE AND RISK OF FRACTURE

Increased BTM levels predict fragility fractures independently of age, BMD, and prior fracture in prospective cohort and case-control studies. This association has been

Key words: bone turnover, osteocalcin, C-terminal cross-linking telopeptides of type I collagen, deoxypyridinoline, osteoporosis
TABLE I. DETERMINANTS OF THE PREANALYTICAL VARIABILITY OF BONE TURNOVER

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found in postmenopausal and elderly women, but not in the frail elderly where incident falls were the strongest predictor of fracture. BTM levels are predictive of all fractures, vertebral fractures, hip fracture, and multiple fractures. The fractures are predicted mainly by the bone resorption markers and BALP but not by less specific BTMs (total alkaline phosphatase, hydroxyproline). Analysis of three major predictors (i.e., BMD T-score < −2.5, CTX above premenopausal values). (Reproduced with kind permission of Springer Science and Business Media from Johnell O, Oden A, de Laet C, Garnero P, Delmas PD, Kanis JA 2002 Biochemical indices of bone turnover and the assessment of fracture probability. Osteoporos Int 13:523–526.)

FIG. 1. Ten-year probability of hip fracture in Swedish women according to age and relative risk. The symbols show the effect of risk factors on fracture probability derived from women 65 (OFELY study) or 80 yr of age (EPIDOS study). Data from the OFELY study are derived from information on all fractures. The following threshold values were used for the risk factors: low BMD, T-score < −2.5; high CTX, above premenopausal values. (Reproduced with kind permission of Springer Science and Business Media from Johnell O, Oden A, de Laet C, Garnero P, Delmas PD, Kanis JA 2002 Biochemical indices of bone turnover and the assessment of fracture probability. Osteoporos Int 13:523–526.)

ular compartment (trabecular perforations, loss of trabeculae, poor trabecular connectivity) and in the cortical compartment (cortical thinning, increased porosity). Thus, women with high bone turnover experience more severe decrease in bone strength. However, they may also have experienced a higher bone loss and greater structural weakening of bone since achievement of their peak bone mass. Consequently, remaining bone may sustain higher stress, leading to a more rapid fatigue of bone tissue and the deterioration of its material mechanical properties. Resorption cavities trigger stress risers, leading to the local weakening of the trabecula. High bone turnover is associated with a higher fraction of recently formed partly mineralized bone, which may have suboptimal mechanical resistance. Shorter periods between metabolic cycles leave less time for the post-translational modifications of bone matrix proteins (cross-linking, β-isomerization of collagen type I). Low isomerization of type I collagen, assessed by the α/β ratio of urinary CTX, was associated with a higher risk of fracture independently of other predictors, including the bone turnover rate. Thus, the maturation of bone matrix may play a role in the skeletal fragility.

BIOCHEMICAL BTMs AND ANTI-OSTEOPOROTIC TREATMENT

In pharmaceutical trials, BTMs provide information on the metabolic effect of drugs on bone turnover, help to establish
the adequate dose, and predict the increase in BMD and the decrease in the fracture risk. Their use may improve compliance to treatment.

METABOLIC EFFECT OF ANTI-OSTEOPOROTIC TREATMENT

Changes in BTM levels depend on the mechanism of action of the drugs. Inhibition of bone resorption by antiresorptive drugs results in a rapid decrease in bone resorption (Fig. 2). As bone formation continues in BMUs activated before treatment, bone formation is stable and then decreases when osteoblasts fill in the lower number of BMUs formed during treatment. BMD increases rapidly during the early period, when bone resorption is reduced and bone formation is still at the baseline level. Changes in BTMs during antiresorptive therapy depend on the route of administration and dose of the drug, degree of inhibition of bone resorption, and the cellular mechanism of action of the drug. For instance, intravenous bisphosphonates decrease BTM levels faster than when orally administered.

During bone formation-stimulating treatment, recombinant human PTH(1-34) (teriparatide) induced a rapid increase in bone formation (especially PINP) followed by an increase in bone resorption. BMD increases rapidly during the early phase and mainly in trabecular bone. Strontium ranelate slightly increases BALP and slightly lowers serum CTX-I at the beginning of the therapy, and then both plateau throughout treatment.

DOSE-FINDING STUDIES

BTMs help to establish the appropriate dose of anti-osteoporotic drugs because the treatment-induced changes in BTM are more rapid compared with BMD. Oral antiresorptive drugs induce a dose-dependent decrease in bone resorption (3 mo) and bone formation (6 mo), followed by an increase in BMD (1 yr). The higher the dose, the lower the steady-state BTM level and the higher the increase in BMD. Such trends are observed for transdermal 17β-estradiol, raloxifene, alendronate, risedronate, and ibandronate.

The first dose of intermittent treatment with subcutaneous monoclonal anti-RANKL antibody (denosumab) or intravenous bisphosphonates induces a very rapid dose-dependent decrease in bone resorption. The higher the dose of the drug, the longer the period of the decreased bone resorption, the lower the levels of bone resorption markers before injection of the drug, and the higher the increase in BMD.

During treatment with bone formation-stimulating PTH, dose-dependent increases in BMD and BTM levels are also observed, especially for lumbar spine BMD and bone formation markers.

DECREASE IN BTM LEVELS AND ANTIFRACTURE EFFICACY OF ANTIRESORPTIVE TREATMENT

Changes in BMD induced by antiresorptive therapy are weakly associated with their antifracture efficacy. For any change in BMD, fracture risk is lower in the treated than in the placebo group. Thus, BMD is a poor surrogate measure of the antifracture efficacy of this treatment. The early decrease in BTM levels (6-12 mo) is associated with the long-term antifracture efficacy of the antiresorptive agent. For a given decrease in BTM levels and for a given BTM level during treatment, the incidence of vertebral fracture was similar in the active treatment and placebo groups.

BTM LEVELS AND ANTIFRACTURE EFFICACY OF BONE FORMATION-STIMULATING TREATMENT

Teriparatide-induced early increase in BTM levels is correlated positively with the subsequent increase in BMD, especially with the increase in trabecular volumetric BMD, probably because there are more BMUs in the trabecular bone.

CHANGES IN BONE TURNOVER AFTER DISCONTINUATION OF ANTI-OSTEOPOROTIC TREATMENT

Hormone replacement therapy (HRT) is active during its administration. Discontinuation of HRT results in a rapid increase in BTM levels to the pretreatment level and is followed by a decrease in BMD and an increase in fracture risk. Bisphosphonates have a strong affinity to bone, are accu-
mulated in bone, and are not metabolized. After withdrawal of short-term treatment (ibandronate, 9–12 mo), BTMs increased rapidly. The lower the cumulative dose, the sooner the BTMs returned to baseline. After withdrawal of alendronate administrated for several years, BTM increased moderately and BMD decreased more slowly. Withdrawal of PTH(1-84) after 1 yr of treatment was followed by a return of BTM levels to baseline values and a decrease in volumetric BMD of trabecular bone. COMBINATION THERAPY AND BTMs

Three designs combining antiresorptive and PTH have been studied in postmenopausal women: both drugs administered jointly, antiresorptive treatment followed by PTH, and PTH followed by antiresorptive treatment.

Alendronate and PTH(1-84) administrated jointly rapidly decreased bone resorption (serum CTX-I) but less than alendronate alone and temporarily increased bone formation (PINP, BALP) but less that PTH(1-84) alone. Then, bone formation decreased and remained slightly below baseline levels. The time course of BTM levels during this therapy was more strongly determined by alendronate, which is consistent with the similar changes in BMD in the combination therapy group and in the group receiving alendronate alone.

The effect of PTH treatment on BTM levels after antiresorptive treatment depends on the degree of inhibition of bone turnover. After a strong suppression of bone resorption by alendronate, the increase in BTM levels induced by teriparatide was delayed and smaller than after raloxifene therapy. In the women treated with risedronate, BTMs were higher, and teriparatide induced a greater increase in BTMs than in those treated with alendronate.

Alendronate administrated after PTH(1-84) induces a marked decrease in BTM levels that are indistinguishable from those in women treated with alendronate alone. This strong inhibition of bone turnover may prevent the resorption of the bone synthesized under PTH(1-84) treatment, which results in an additional increase in BMD.

ASSOCIATION BETWEEN BTM LEVELS AND ADHERENCE WITH ANTIRESORPTIVE TREATMENT

Low compliance is a serious problem during anti-osteoporotic treatment, leading to an increased risk of fracture. BTM change reflects the degree of compliance to risendronate treatment in postmenopausal osteoporotic women. The better the compliance, the greater the average decrease in bone turnover. Moreover, measurement of BTM levels may also improve the persistence with antiresorptive treatment (e.g., risk of treatment discontinuation was lower in women who received positive information corresponding to a >30% decrease in NTX-I urinary excretion).

BTMs IN MEN

In boys, the growth spurt starts later and lasts longer than in girls. Therefore, young men enter the phase of consolidation (formation of peak BMD after growth arrest) later than women. Men have wider bones even after adjustment for body size. At the age of 20–25 yr, men have BTM levels higher than women because men have more active bone turnover in longer and wider bones. Then, BTMs decrease and attain their lowest levels between 50 and 60 yr of age. After the age of 60, bone resorption remains stable or increases slightly. Bone resorption increases progressively after the age of 60. However, bone resorption markers, which have produced meaningful data in women, do not necessarily reflect the status of bone resorption in elderly men. Men with high bone turnover have lower BMD, thus, age-related bone loss in men results at least in part from increased bone resorption. Elderly men with high BTM levels have a faster subsequent bone loss; however, this association is weak. In a nested case-control study, a high level of CTX-MMP (ICTP) was associated with an increased risk of incident clinical fractures. Recent prospective large cohort studies showed that BTMs do not predict osteoporotic fractures in elderly men.

EFFECT OF ANTI-OSTEOPOROTIC TREATMENT ON BTM IN MEN

Testosterone replacement therapy (TRT) inhibits bone turnover in hypogonadism if the normal bioT concentration has been achieved. During TRT, bone resorption decreases promptly, but decrease in urinary excretion per milligram creatinine may be partly related to the increase in muscle mass. Bone formation increases during the first 6 mo of TRT (direct stimulatory effect), levels off, and finally decreases, reflecting the general slowdown of bone turnover. The equivalent daily doses of bisphosphonates (alendronate 10 mg, risedronate 5 mg) similarly decreased BTMs in men with low BMD and in elderly men after stroke. In men, teriparatide increased bone formation (PINP) after 1 mo and bone resorption after 3 mo of treatment. In growth hormone (GH)-deficient men, recombinant human GH accelerated bone turnover. BTMs attained their peak values after 6–12 mo and then decreased progressively.

CONCLUSIONS

BTMs improve our understanding of the relationship between bone turnover, BMD, bone fragility, and the effect of anti-osteoporotic treatment (metabolic effect, antifracture efficacy). Data on BTMs show that the rate of bone turnover (spontaneous or modified by the therapy) is an important determinant of bone fragility in postmenopausal and elderly women. Preliminary data suggest that the use of BTMs may improve the cost-effectiveness of the anti-osteoporotic treatment. From a clinical point of view, measurement of BTMs may help to identify postmenopausal women at high risk of fracture and may improve persistence with antiresorptive treatment. However, practical guidelines for the use of BTMs in the clinical management of postmenopausal osteoporosis are still lacking.

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