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Capture the fracture – Use of bone turnover markers in clinical practice

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SUMMARY
Bone is a living tissue, metabolically very active, with the level of turnover of about 10% per year. Bone remodeling is a well-balanced process of bone resorption, induced by osteoclasts and bone formation-maintained osteoblasts. Loss of bone remodeling balance, with increased bone resorption, leads to osteoporosis. Bone turnover markers are classified as markers of bone formation and of bone resorption. During the growth and development of skeleton, bone turnover markers show higher levels of activity than in the adult period. The increase in biochemical markers peaks again in the postmenopausal period, indicating accelerated bone remodeling. Bone mineral density is an important predictor of an osteoporotic fracture. Timely assessment of risk factors of osteoporosis and bone markers can detect subjects with accelerated bone remodeling and osteoporosis. This may introduce adequate therapy and prevent fracture.
Keywords: bone; bone markers; osteoporosis; fracture

INTRODUCTION

Bone is metabolically active tissue that undergoes continuous remodeling by two counteracting processes, namely bone formation and bone resorption. These processes rely on the activity of osteoclasts (resorption), osteoblasts (formation), and osteocytes (maintenance). Bone cells secrete enzymes and proteins, detected in serum and urine, named bone turnover markers (BTMs) [1]. Under normal conditions, the resorption phase takes approximately 10 days, which is then followed by a formation phase that can last for up to three months. Bone turnover is the principal factor that controls both the quality and the quantity of bone in the adult skeleton. High bone turnover, characterized by increased activity of osteoclasts, leads to bone loss, abnormal bone micro architecture and potential deterioration in bone quality. Low bone turnover, characterized by a reduction of both bone formative and bone resorptive activities may result in increased bone mass, accumulation of micro-damage and bone fragility [2]. Unbalanced bone turnover leads to osteoporosis, a systemic skeletal disease characterized by low bone mass and micro architectural bone deterioration, with consequent increase in bone fragility.

Bone comprises about two thirds mineral and one third osteoid, most of which is type I collagen. Pyridinium's cross-linking molecules stabilize the collagen triple helix in mature bone. During resorption, fragments of type I collagen enter the circulation, and are then cleared in the urine. The collagen-derived bone resorption markers in clinical use do not reflect dietary intake and are relatively specific for bone. Changes in BTMs, which include bone resorption and bone formation markers, are dynamic. The aim of this paper is to review the application of BTMs in the management of osteoporosis.

What are the bone turnover markers?

BTMs are biochemical products, measured usually in blood or urine, which reflect the metabolic activity of bone. Pioneering work in the mid-1990s indicated that measurement of BTMs provided insight into bone turnover rates, which correlate well with bone resorption and formation [3]. BTMs can be divided into bone resorption and bone formation markers, as shown in Table 1. They are used in identifying subjects with an increased risk of fractures and for monitoring treatment of osteoporosis or bone metastases.

Table 1. Markers of bone remodeling in serum

Bone resorption markers	Tartrate-resistant acid phosphatase (TRAP)
	C-terminal telopeptide fragment of type I collagen (CTP)
	β-crosslaps (βCTX)
	N-terminal telopeptide fragment of type I collagen (NTX)
Bone formation markers	Total alkaline phosphatase (ALP)
	Bone alkaline phosphatase (bsALP)
	Osteocalcin (OC)
	C-terminal propeptide of protocollagen type I (P1CP)
	N-terminal propeptide of protocollagen type I (P1NP)

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Markers of bone formation

Bone formation markers in serum are released from osteoblasts, during bone matrix synthesis. They consist of matrix proteins (osteocalcin), products of posttranslational processing of type I collagen molecules (procollagen type I N- or C-terminal propeptides) and enzymes (alkaline phosphatase).

Alkaline phosphatase has been clinically available for several years as a marker for bone metabolism. Total serum alkaline phosphatase consists of several dimeric isoforms that originate from various tissues, such as liver, bone, intestine, spleen, kidney, and placenta. In adults with normal liver function, approximately 50% of the total alkaline phosphatase activity arises from the liver and 50% from the bone [4]. Higher serum values can be found in osteoporosis, hyperparathyroidism, osteosarcoma, bone metastases, Paget's disease; mild elevation can be found in liver disease, Hodgkin's disease, ulcerative colitis. The development of immunoassay-based markers with monoclonal antibodies directed to the bone-specific isoform of alkaline phosphatase has improved specificity and sensitivity [5]. Bone-specific alkaline phosphatase is more specific to represent function of osteoblasts and is elevated in bone mineralization [6]. Changes in bone-specific alkaline phosphatase can lag by several weeks. The half-life of bone-specific alkaline phosphatase is two days, and is less sensitive to circadian variation. The proposal is to measure and monitor alkaline phosphatase at the beginning of the treatment of osteoporosis and after three and six months.

Osteocalcin (OC) or bone Gla-protein (glutamic acid) is the main non-collagen protein of the bone matrix, which is primarily synthesized by osteoblasts, odontoblasts, and hypertrophic chondrocytes. It contains 49 amino acids (5.8 kDa), of which there are three gamma-carboxyl glutamic acids (post-translational, K vitamin-dependent enzyme carboxylation) at positions 17, 21, and 24, and they are responsible for calcium-binding characteristics of this protein. Osteocalcin binds to hydroxyapatite and constitutes 15% of non-collagenous osteoid. It is a late marker of bone formation. Elevated OC values are described in patients suffering from increased bone formation – hyperparathyroidism, Paget's disease, significant remodeling due to osteoporosis, hyperthyroidism, renal osteodystrophy, fractures, and acromegaly. It is also elevated in postmenopausal women with high bone turnover [7]. This peptide is rapidly degraded in serum; its fragments can be detected by antibody-based assays. Because it is very quickly secreted through kidneys, the half-life of circulating OC is around four to five minutes. OC and its fragments accumulate and their concentration in serum increases when kidney function is changed. Osteocalcin has circadian rhythm activity, being higher in the morning. Hence, it is recommended to take serum samples of osteocalcin at the same time, in the morning, best before 9 a.m. [8]. Osteocalcin values may be affected by anticoagulant drugs. Osteocalcin should be monitored at the start of osteoporotic therapy and after three and six months.

Procollagen type-1 N-terminal propeptide (P1NP) represents a marker of type I collagen synthesis, circulates as a trimeric structure and soon exceeds in the monomeric form. It primarily appears from osteoblasts, but small amounts derive from skin, tendon, dentin and cartilage [9]. It follows a low diurnal rhythm, higher in early morning; concentration is not dependent of renal function. P1NP is cleared by the mannose receptor in endothelial cells of the liver, regulated by growth hormone and thyroid hormones. Interpretation of results is complicated in patients with pituitary or thyroid diseases [10]. P1NP is inversely associated with bone mineral density (BMD) even after controlling for age, body mass index, and years since menopause. The utility of P1NP in the management of metabolic bone diseases remains a subject of debate since the reference ranges are not rigorously established [11].

Markers of bone resorption

Markers of bone resorption are generated from type I collagen, by the protease, cathepsin K, in osteoclasts. Type I collagen comprises more than 90% of the protein of the bone. The most commonly used markers of bone resorption are C-terminal cross-linked fragment of type I collagen (CTX-1) and N-terminal cross-linked fragment of type I collagen (NTX). Two types of CTX-1 may be analyzed as the α and β type. αCTX-1 is generated by cathepsin K cleavage during osteoclast-mediated bone resorption of young collagen. It is elevated in cases with very high bone turnover, such as Paget's disease, osteolytic metastases, osteoarthritis, and rheumatoid arthritis. βCTX-1 is generated during the resorption of mature collagen. The index of αCTX/βCTX represents the ratio of bone remodeling. Both may be used as a potential indicator of risk of osteonecrosis of the jaw in patients receiving oral bisphosphonates [12].

Since the levels of serum NTX and CTX are significantly reduced during anti-resorptive therapy, both are helpful in monitoring the treatment of osteoporosis. The recommendation is to analyze them before treatment and after three and six months. These markers follow the circadian rhythm, being higher early in the morning. Hence, plasma samples should be taken before 9 a.m. These values are not dependent on food intake [13]. The importance of bone resorption markers is underlined by the fact that changes can be observed markedly earlier than the BMD changes, i.e. CTX level measured at three months is predictive of a three-year change in BMD [14]. However, low levels of βCTX may be maintained long after the cessation of therapy.

Pyridinium cross-links and deoxypyridinoline are found in mature collagens and are involved in the cross-linking between collagen polypeptides. They can be detected in urine and serum [15]. These markers also follow circadian rhythm and are higher early in the morning and scarcely influenced by diet. Their use in clinical practice is limited due to low sensitivity.

Tartrate-resistant acid phosphatase 5b (TRACP-5b) and cathepsin K are enzymes produced by osteoclast during

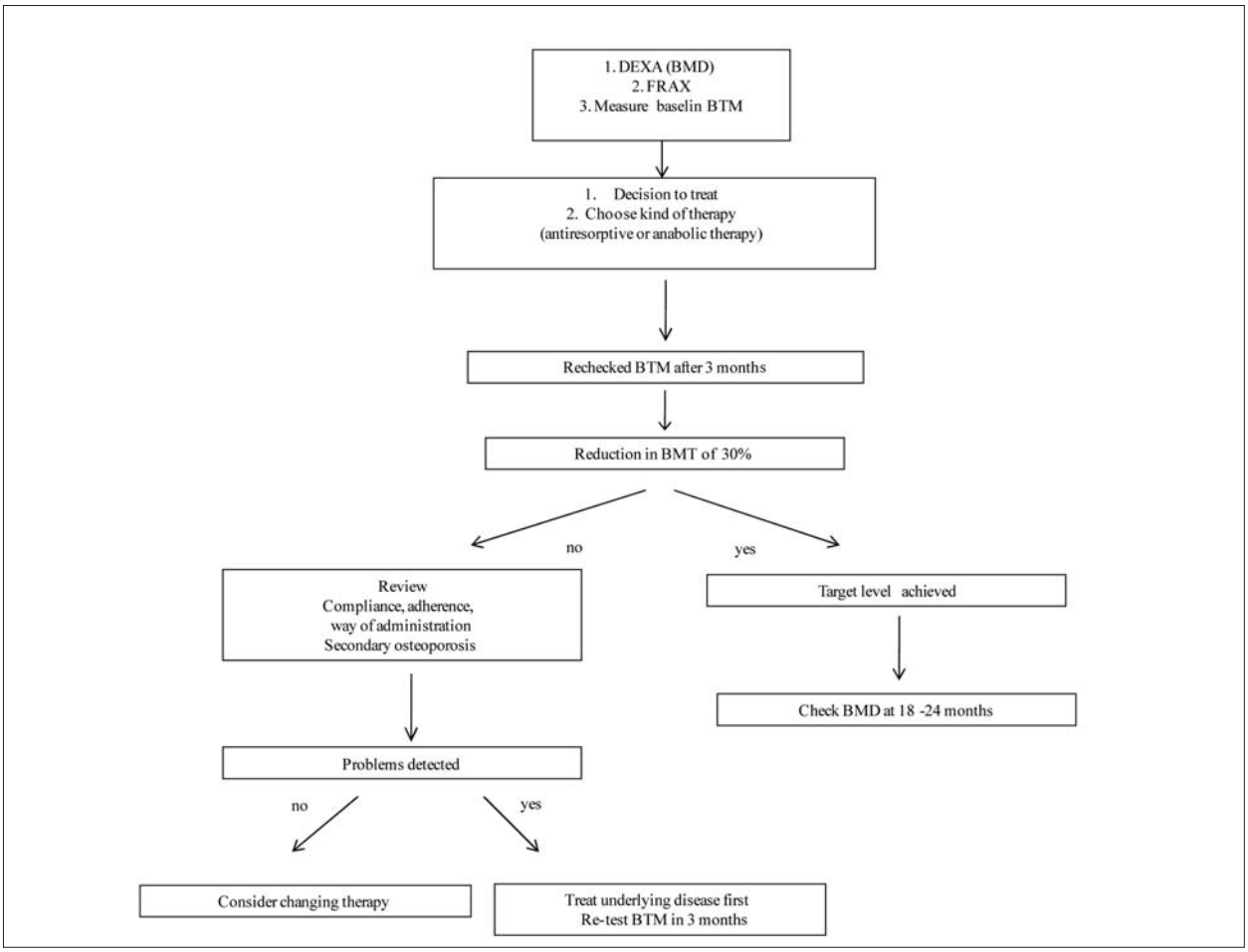
bone resorption. They reflect osteoclast number. TRACP-5b is typically increased in high bone turnover conditions, such as Paget's bone disease, bone metastases, multiple myeloma and after ovariectomy [16]. Its sensitivity to report changes in bone turnover after anti-resorptive therapy has not been as consistent as with other markers, so it has not been viewed as reliable in monitoring osteoporosis.

Bone sialoprotein is the most important non-collagenous extracellular matrix protein, in addition to osteocalcin and osteonectin. It is involved in the mineralization of newly deposited bone matrix and in tissue extra-skeletal calcification. It is a highly phosphorylated acidic glycoprotein with high affinity for hydroxyapatite crystals. Its level reflects the level of bone resorption [17].

USE OF BONE TURNOVER MARKERS IN DIAGNOSIS AND FRACTURE RISK ASSESSMENT

Bone turnover markers are increased in women after menopause, correlating well with accelerated bone turnover. However, the diagnosis of osteoporosis is made by BMD, as biomarkers of tissue turnover do not provide a stand-alone diagnostic value. An inverse correlation, dependent on skeletal site and age, has been observed between BMD and BTMs, but this is stronger for resorption than for formation markers. BTMs are a helpful tool in assessment of bone remodeling in patients with osteopenia (low normal BMD). In osteopenic patients, assessment of risk factors for osteoporosis and measurement of BTMs may detect those with an increased fracture risk, who would benefit from early therapy [18]. The OFELY study has shown a10-year expectancy of fracture in osteopenic women with one risk factor of 26%, compared to 6% in women with no risk [19].

High levels of bone turnover markers are associated with an increased risk of fracture, independent of BMD. Several studies have shown that independent risk factors for spine and hip fractures are elevated CTX. Women with osteoporosis of hip and high serum CTX levels have a fracture risk of 55% in five years. When there is low BMD with normal CTX, the risk is 39%, and when only isolated high CTX levels are present, the relative risk is 25% [19]. High urinary deoxypyridinoline positively correlates with hip fracture risk [20]. A meta-analysis of several randomized clinical trials, evaluating the treatment of osteoporosis, has shown that a reduction in bone resorption markers of 70% reduces non-vertebral fracture risk for 40%. A 50% decrease in bone formation markers was associated with a 44% reduction for non-vertebral fracture risk [21].



Scheme 1. An algorithm for the use of bone turnover markers (BTMs) in treatment and monitoring of osteoporosis (adapted from and based on Bergmann et al. [31])

DEXA – dual energy X-ray absorptiometry; BMD – bone mineral density; FRAX – fracture risk assesment tool; BTM – bone turnover markers

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Table 2. Uncontrollable and controllable sources of variability on bone turnover markers (BTMs) and their importance (adapted from and based on Bergmann et al. [31])

	Very important		Important	
Uncontrollable source of variability on BTMs	Age	BTMs increase with age in men and women	Fractures	BTMs increase after a fracture (maximal at 2–12 weeks, but effect lasts for up to 52 weeks)
	Menopause	BTMs increase within a few months after the last menstrual period	Pregnancy, lactation	BTMs are increased during pregnancy; highest levels during third trimester, even higher postpartum
	Sex	BTMs are higher in older women than in older men	Drugs (corticosteroids, anticonvulsants, heparin, GnRH agonists)	BTMs may be decreased (glucocorticoids) or increased (anticonvulsants)
			Disease (thyroid disease, diabetes, renal impairment, liver disease)	BTMs often increased (thyrotoxicosis, chronic kidney disease)
			Bed rest/immobility	Bone formation markers decrease and resorption markers increase
Controllable source of variability on BTMs	Circadian	Most striking for bone resorption markers; highest values in second half of night and on waking; lowest values in afternoon and evening	Fasting status	Feeding results in a decrease in BTMs; for example, s-CTX decreases by 20% after breakfast
			Exercise	Changes occur but depend on type of exercise and age of subjects

In clinical practice, the use of BTMs should be carefully considered, and all their causes should be taken into account in their interpretation (Table 2). Assessment of parameters of bone metabolic activity is important to differentiate physiological from pathological bone metabolism. For example, an increase in BTMs of more than 150% of the upper reference range is not typical of postmenopausal osteoporosis and should prompt a search for another cause. Often, these levels are indicative of other diseases, even metastases [22].

BONE TURNOVER MARKERS IN MONITORING THERAPEUTIC EFFICACY AND ADHERENCE TO THERAPY

Bone resorption markers rapidly decrease by over 40% after three months of bisphosphonate therapy. This is followed by a reduction in bone formation markers in the next six months [23]. Changes in BTMs predict changes in BMD. A decrease in CTX after three months on ibandronate is predictive of a significant increase in BMD of lumbar spine after one and two years [24]. Recent data for zoledronic acid have shown good result in reduction in alkaline phosphatase, P1NP, CTX levels, which precedes the reduction in vertebral fractures [25]. Bone resorption markers remained low even after six years of treatment [26]. Similar result has been shown with denosumab, which produces a very rapid fall in resorption markers and a smaller change in formation markers. Low levels are maintained on therapy [27, 28]. In contrast, teriparatide treatment stimulates new bone formation. Bone formation markers are doubled during the first month of treatment and continue to increase in the following six months [29].

Lack of efficacy may be the reason for no change in BTMs on anti-resorptive therapy. Sometimes, the reason for non-reduction of BTMs is poor compliance with therapy, secondary osteoporosis, malabsorption, or eating too soon after taking oral bisphosphonates. This problem can be solved by switching to parenteral form of therapy or changing to a different class of medication [30]. An algorithm has been proposed for the use of bone turnover markers in treatment and monitoring of osteoporosis (Scheme 1).

Adherence to bisphosphonate therapy is not easy. Taking a weekly or monthly medication can easily be forgotten. Compliance and persistence in osteoporosis is not significantly different from other asymptomatic chronic conditions. Most of the poor medication behavior with osteoporosis medication is probably intentional rather than unintentional. Low suppression of BTMs can be indicative of non-compliance. Some studies have shown improved adherence to treatment when turnover marker results were provided to patients [32].

There is still no consensus on the duration of bisphosphonate therapy. A "drug holiday" in low-risk patients after five years of continuous treatment with bisphosphonates has been proposed [33]. In clinical practice, recheck of BTMs at six-month intervals of drug holiday may indicate the need to start the therapy again. This is done when BTMs increase to the upper limit of the premenopausal range.

PRECAUTION AND SELECTION OF SPECIFIC THERAPY

BTM variation includes diurnal and circadian variability. Diurnal variability of bone markers may be as high as 40–70%, whereas the circadian is 7–17%. Levels of BTMs are the highest in the early morning and the lowest in the afternoon and evening. It is worth mentioning that an increase in dietary calcium intake can lower the levels of BTMs, particularly in people with low calcium intake [34]. The range for BTMs must be adjusted for sex and age. Physical activity can increase BTMs [35]. The

lack of assay standardization is still a matter of concern, making difficult the comparison of results obtained by different methods or laboratories. This is the reason why monitoring should always be done in the same laboratory. Theoretically, better response to anti-resorptive therapy is expected in patients with high bone turnover (higher levels of BTMs), while an anabolic agent would be more appropriate in case of low bone turnover. However, the use of BTMs in selection of the optimal treatment for osteoporosis is not recommended [36].

CONCLUSION

Bone turnover markers have clinical applicability in decision making on early treatment of women with osteopenia, fracture risk assessment, and monitoring of therapy. They could identify "fast bone losers", which could benefit the most from the therapy, and "non-responders", which could benefit from the change of therapy. To capture the fracture is possible with timely measurements of bone mineral density and bone turnover markers.

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Спречити фрактуру – употреба коштаних маркера у клиничкој пракси

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КРАТАК САДРЖАЈ

Кост је живо ткиво, метаболички врло активно, са коштаним обртом од око 10% годишње. Коштано ремоделовање представља равнотежу између процеса ресорпције и формирања кости, регулисану активношћу остеокласта и остеобласта. Губитком равнотеже између ова два процеса, са преовладавањем процеса ресорпције у односу на процес формирања кости, настаје остеопороза. Маркери коштаног промета су класификовани у маркере формирања и маркере ресорпције кости. Током раста и развоја скелета, биохемијски маркери показују виши ниво активности него код одраслих. Пораст нивоа коштаних маркера јавља се поново у постменопаузалном периоду, услед недостатка естрогена, што индикује убрзање коштаног ремоделовања. Минерална густина кости је важан предиктор ризика за прелом. Важно је на време испитати факторе ризика за остеопорозу и тестирати коштане маркере. Правовремено откривање особа са убрзаним коштаним ремоделовањем и увођење терапије може спречити настанак остеопоротичне фрактуре.

Кључне речи: кост; коштани маркери; остеопороза; фрактура

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