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Review

Clinical utility of bone turnover markers in the management of common metabolic bone diseases in adults

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ABSTRACT

Bone turnover marker (BTMs) concentrations in blood and urine reflect bone-remodelling activity, and may be useful adjuncts in the diagnosis and management of metabolic bone diseases. Newer biomarkers, mainly bone regulatory proteins, are currently being investigated to elucidate their role in bone metabolism and disease and may in future be useful in clinical diagnosis and management of metabolic bone disease. BTM concentrations increase around menopause in women, and at a population level the degree of increase in BTMs reflect bone loss. However, lack of adequate data precludes their use in individual patients for fracture risk assessment in clinical practice. The rapid and large changes in BTMs following anti-resorptive and anabolic therapies for osteoporosis treatment indicate they may be useful for monitoring therapy in clinical practice. The offset of drug effect on BTMs could be helpful for adjudicating the duration of bisphosphonate drug holidays. BTMs may offer useful additional data in skeletal diseases that are typically characterised by increased bone remodelling: chronic kidney disease (CKD), primary hyperparathyroidism (PHPT) and Paget's disease. In CKD, bone specific alkaline phosphatase (bAP) is currently endorsed for use for the assessment of mineral bone disease. The role of BTMsin predicting the bone mineral density response to successful parathyroidectomy in PHPT shows some utility but the data are not consistent and studies are limited in size and/or duration. In Paget's disease of bone, BTMs are used to confirm diagnosis, evaluate extent of disease or degree of activity and for monitoring the response to bisphosphonate treatment. Whilst BTMs are currently used in specific clinical practice instances when investigating or managing metabolic bone disease, further data are needed to consolidate their clinical use where evidence of utility is limited.

1. Introduction

BTM concentrations in blood and in urine are thought to reflect bone-remodelling activity and are preferred to more invasive techniques such as bone histomorphometry or calcium kinetic studies to evaluate skeletal turnover. Bone turnover maker concentration reflects the overall activity of the whole skeleton, including cortical and trabecular bone compartments as opposed to histomorphometry which is specific to the area from where the biopsy is taken [1].

Whilst BTMs are classified as bone formation markers (BFM) and bone resorption markers (BRM) based on the phase of the bone remodelling cycle they are thought to reflect, resorption and formation are “coupled” and therefore in most circumstances the changes in BFM and BRM are synchronous in adults. Exceptions to this rule include multiple myeloma where resorption is increased without an increase in formation, and osteoblastic secondaries of prostate and some breast cancers in which bone formation may be increased to a greater extent than resorption.

In this review we examine the possible role of BTMs in the management of four important and most common metabolic bone diseases in adults. We then summarise briefly the measurement of the two most commonly used BTMs and of another two markers that may potentially have utility in assessing metabolic bone disorder in chronic kidney disease (CKD-MBD), in which most other BTMs are compromised.

1.1. History

Pierre Delmas, a pioneer in the field of bone markers, stated in 1990 “the development of a battery of several bone-specific markers that indicate various aspects of the complex mechanisms of bone formation, resorption, and mineralization is likely to provide new tools for the diagnosis and management of bone diseases” [2]. Osteocalcin (OCN) or bone Gla protein was one such marker. Bone specific alkaline phosphatase (bAP) and the bone specific isoform of acid phosphatase

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Table 1
Bone turnover markers.

Bone formation markers	Bone resorption markers
Blood	Blood
Procollagen I N terminal extension pro-peptide (PINP)	C-terminal type I collagen telopeptide (CTX)
Osteocalcin (OCN)	C terminal telopeptide (ICTP)
Procollagen I C terminal extension peptide (P1CP)	Tartrate resistant acid phosphatase 5b (TRACP5b)
Bone specific alkaline phosphatase (bAP)	
	Urine
	N-terminal type I collagen telopeptide (NTX)
	Deoxypyridinoline (DPD) free or total
	Hydroxyproline (obsolete)

(tartrate resistant acid phosphatase 5b, TRACP5b) were identified as enzyme products of osteoblast and osteoclast respectively, and therefore reflecting their activity. Hydroxyproline in urine (u-OHP) was one of the first collagen degradation products measured to assess bone turnover although it is found in skin and other tissues and therefore not bone specific. Assays for pyridinium crosslinks and the telopeptides of the collagen 1 molecule for bone resorption and the procollagen 1 propeptides for formation were developed and have proven to be reasonably specific to bone (Table 1).

1.2. Newer bone biomarkers

Among newer markers of bone metabolism, the most studied is periostin, a protein mainly expressed by periosteal osteoblasts and osteocytes and that may be a marker of periosteal metabolism, but which is not specific to bone tissue [3]. Periostin in serum has shown a weak correlation with bone density or fracture in postmenopausal women in some (but not all) studies [3,4]. Further studies with assays specific to a bone isoform of periostin may be useful in elucidating its clinical use in the management of bone disease [5]. Other proposed newer markers include Cathepsin K, an osteoclastic enzyme, and micro RNAs [3].

The molecular mechanisms for the osteoblast-osteoclast interaction which drive osteoclast differentiation and action have been well characterised in recent times [6] and measurement of the factors involved have been explored as markers of bone metabolism. These pathways are illustrated in Fig. 1. The main cell signalling molecules which are involved in bone resorption are members of the tumour necrosis factor (TNF) and TNF receptor super family. The receptor activator of NF-kappaB ligand (RANKL), which is secreted by osteoblasts binds to receptor activator of NF-kappaB (RANK) found on osteoclast precursor cells and osteoprotegerin (OPG), a decoy receptor for RANKL, which blocks RANKL/RANK interactions. RANKL expression by osteoblasts is upregulated by stimulators of bone resorption, and conversely OPG expression is downgraded. However, OPG may also increase in response to an increase in bone resorption and the resulting bone loss such as in aging [6]. Sphingosine-1-phosphate (S1P), a sphingolipid metabolite, is a mediator molecule with diverse effects on multiple biological processes that potentiates osteoclastogenesis via the RANKL pathway.

An important regulator of osteoblastic bone formation is the glycoprotein sclerostin, a product mainly of osteocytes [7]. Sclerostin binds to the low-density lipoprotein receptor-related proteins 5 and 6 on osteoblasts and inhibits canonical Wnt/β-catenin signalling and reduces bone formation. Dickkopf (DKK) is also an inhibitor of the Wnt signalling pathway and plays an important role in osteoblastogenesis and osteoblast action.

Whilst studies have examined the association of these molecules with bone disease, there are insufficient data at present to recommend their measurement in clinical practice for management of metabolic bone disease [3].

As with all analytes in blood, and to a greater extent in urine, BTMs show both biological and analytical variation, and this has been well studied and characterised [8,9]. Some markers are affected by food and circadian rhythm to a greater extent than others. Therefore, the recommendation is to collect samples for BTM measurement in the fasting state at a fixed time in the morning [10].

2. Osteoporosis

Osteoporosis is defined as “a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk” [11]. Osteoporosis develops with aging and in postmenopausal women, as a result of bone loss brought about by an imbalance between bone formation and bone resorption. This also results in deterioration of bone microstructure and loss of bone strength leading to increased fragility or propensity to fracture. Although menopause and aging are natural processes, there is a large variability between individuals; fracture is not regarded as a physiological effect of either and bone loss is accentuated by many diseases and medications.

2.1. Prediction of bone loss

Menopause is characterised by an increase in remodelling attributed to the loss of oestrogen activity [9]. The increase in BTMs demonstrable at menopause is associated with an imbalance in bone resorption and formation, with the increase in BRM being greater than and preceding the increase in BFM and sustained even in late menopause [9,12]. Bone loss at menopause and later in postmenopausal women may be explained by this increase and imbalance in bone resorption and formation. Population-based studies show a negative correlation between BTMs and bone mineral density (BMD) [13]. However, at an individual level, BTMs are not useful in predicting BMD or bone loss with any degree of accuracy in postmenopausal women [9], or for that matter in elderly men.

2.2. Prediction of BMD

The diagnosis of osteoporosis is based on a BMD T score of ≤ 2.5. BTMs have no role in the diagnosis of osteoporosis. Some studies have shown a significant inverse relationship between BTMs and BMD in postmenopausal women, and elderly men [13,14]. However, BTMs have no value for the prediction of BMD or the diagnosis of osteoporosis in individual patients [15].

2.3. Fracture prediction

Treatment decisions to reduce fracture risk are based among other things on absolute fracture risk prediction. Fracture risk calculators are available for this purpose, and FRAX® (http://www.shef.ac.uk/FRAX) is the most widely used calculator worldwide [16]. Risk factors such as history of prior fracture, family history of fracture, age, BMD and secondary causes of osteoporosis such as rheumatoid arthritis and glucocorticoid therapy, as well as height and weight are included in the FRAX algorithm for the calculation of absolute five or ten year hip and/or total fracture risk. Although BTMs predict fracture risk independent of BMD and some of the other included risk factors [17,18], they are currently not included in the FRAX algorithm as their interactions with all the risk factors included in the calculation are not known due to a dearth of population-based prospective data with any bone marker [19]. More data are need before BTMs can be included in absolute fracture risk calculations. Therefore, BTMs have no role in treatment decisions to assess fracture risk (20). The International Osteoporosis Foundation (IOF) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) joint working group on bone marker standards evaluated the literature and published a position paper