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Review

New developments in biological markers of bone metabolism in osteoporosis

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ABSTRACT

Over the last 15 years several biological markers of bone turnover have been developed with increased specificity and sensitivity. In osteoporosis clinical studies, the IOF and IFCC organizations have recently recommended the measurements of serum type I collagen N-propeptide (PINP) and the crosslinked C-terminal telopeptide (serum CTX) as markers of bone formation and bone resorption, respectively. However these markers have some limitations including a lack of specificity for bone tissue, their inability to reflect osteocyte activity or periosteal apposition. In addition they do not allow the investigation of bone tissue quality an important determinant of skeletal fragility. To address these limitations, new developments in markers of bone metabolism have been recently achieved. These include assays for periostin, a matricellular protein preferentially localized in the periosteal tissue, sphingosine 1-phosphate, a lipid mediator which acts mainly on osteoclastogenesis and the osteocyte factors such as sclerostin and FGF-23. Recent studies have shown an association between the circulating levels of these biological markers and fracture risk in postmenopausal women or elderly men, although data require confirmation in additional prospective studies. Finally, recent studies suggest that the measurements of circulating microRNAs may represent a novel class of early biological markers in osteoporosis. It is foreseen that with the use of genomics and proteomics, new markers will be developed to ultimately improve the management of patients with osteoporosis.

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Introduction

Bone metabolism is characterized by an intimate cooperation of bone cells including osteoblasts, osteoclasts and osteocytes in order to maintain a regulated amount of bone tissue and the integrity of bone structure. In metabolic bone diseases such as osteoporosis, bone metabolism is altered, leading to bone loss, often accompanied by changes in the microarchitecture, leading to bone fragility. The development of serum and urinary assays for biochemical markers reflecting either enzymatic activities of osteoblasts and osteoclasts or breakdown products of bone tissue has been of high value to investigate the complex

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pathways of bone metabolism and their alterations in bone diseases, especially in osteoporosis. They have also helped the clinicians to identify patients at high risk for fracture and to monitor the efficacy of anti-resorptive therapies and bone-forming agents. In the last few years novel biological markers have been developed and studies suggest that they may be valuable research tools for investigating the mechanisms of bone metabolism, to assess the activity of osteocytes and some of them may be of value for the management of patients with osteoporosis. The aim of this paper is to review these novel developments in biological markers of bone metabolism in osteoporosis.

Established biochemical markers of bone metabolism

The structure, biology and clinical utility of conventional biochemical markers in different diseases including osteoporosis has been reviewed in several recent review papers [1–3]. At present, the most specific and sensitive markers of bone formation are serum total osteocalcin; the bone isoenzyme of alkaline phosphatase (bone ALP); and the procollagen type I N-terminal propeptide (PINP), which reflects the rate of synthesis of the main constituent of bone tissue. For the evaluation of bone resorption, most currently available assays are based on the detection in serum or urine of breakdown products of type I collagen. These include the intermolecular crosslinks pyridinoline (PYD) and deoxypyridinoline (DPD), and the cathepsin K (CTX, NTX) and matrix-metalloproteases (MMP)-generated (CTX-MMP or ICTP) type I collagen fragments. Serum 5b isoenzyme of tartrate resistant acid phosphatase (TRACP5b) is also a valuable biochemical marker reflecting mainly the number and the activity of the osteoclasts. Recently an expert group from the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) has performed a comprehensive review of the available data and based on this assessment has recommended the systematic use of serum PINP and serum CTX as reference biochemical markers of bone formation and bone resorption respectively in clinical studies [4]. The current biochemical markers of bone metabolism have however some limitations. These include 1) a lack of tissue specificity for bone, as type I collagen is widely distributed in different organs, 2) an inability to distinguish the metabolic activity of the different skeletal compartments, although they can be differently affected by diseases and treatments, 3) they reflect mainly the function of osteoblast or osteoclast and not the activity of osteocytes although these cells play a pivotal role in the maintenance of skeletal integrity, and 4) they are all protein-based markers, although circulating mRNA could also be of value as early biomarkers.

New biological markers of bone metabolism

Novel markers can be classified in different groups as shown on Table 1 and their involvement in bone cell biology is described on Fig. 1. These include the measurements of some non-collagenous proteins, osteoclastic enzymes other than TRACP5b, osteocyte-secreted factors, molecules involved in the coupling between osteoclast–osteoblasts, and circulating microRNAs. In this paper we will discuss in more details the most promising candidate in each category and their clinical relevance for the investigation of patients with osteoporosis.

Periostin: a matricellular Gla-containing protein as a potential marker of periosteal tissue metabolism?

The periosteum covers long bones and although in adults its metabolism is considered to be low, it plays an important for controlling the diameter of bones and thus bone strength [5]. Currently however there are no available non-invasive biological tools allowing the assessment periosteal metabolism as current bone markers reflect mainly endosteal bone remodeling [6]. The concept of developing biological markers that reflect the remodeling of a particular bone compartment has been suggested for some proteins including osteocalcin which is much more concentrated in the cortical than trabecular bone [7]. Periostin (POSTN), as suggested by its name, may be a candidate marker of periosteal metabolism. A detailed review of the structure, regulation and involvement of this protein in bone metabolism has been recently published [8], but new data have since been generated.

Briefly, the mouse periostin cDNA is 3187 bp long and contains an 18-bp 5′ untranslated region, a 733-bp 3′ untranslated region, and an open reading frame of 2436 bp corresponding to a protein precursor of 838 amino acids. The protein is mainly expressed by periosteal osteoblasts and osteocytes-although osteoclasts may also express low levels [9]. At the protein level it is composed of a signal sequence, followed by an Emilin (EMI) domain rich in cysteine, 4 repeated and conserved Fasciclin-1 (FAS-1) domains, and a C-terminal hydrophilic and variable domain (Fig. 2). Alternative splicing of the C-terminal domain gives rise to at least five different human isoforms. Each FAS-1 domain is rich in glutamate residues and contains an N-terminal recognition site for the vitamin K-dependent enzyme γ-glutamyl carboxylase (γ-carboxylase recognition sites, or CRS) responsible for the posttranslational modification of glutamic residues (Glu) to γcarboxyglutamate (Gla). This protein belongs to the matricellular protein family because it contains binding sites for extra cellular matrix proteins, such as type I and type V collagens, and the cell surface receptor integrins. In adults, POSTN has been shown to be overexpressed at the periosteal surface, but also in other collagen rich tissues subjected to mechanical strain such as periodontal ligaments, heart valves and tendons [8].

The most informative data on the function of POSTN in bone metabolism have been obtained from the examination of POSTN deficient mice. These mice develop periodontis and osteoporosis with lower BMD, altered microarchitecture and decreased bone strength [10]. These studies have also shown that POSTN is an important mediator of the effects of mechanical factors and parathyroid hormone (PTH) on cortical BMD and bone strength by modulating the canonical wnt signaling pathway with a down regulation of sclerostin expression [10,

Table 1
Candidate circulating biological markers of bone metabolism in osteoporosis.

Noncollagenous protein	Osteoclastic enzymes	Regulatory molecules of osteoblasts and osteoclasts	Osteocyte molecules	Micro RNA
Periostin	Cathepsin K	OPG/RANK-L	Sclerostin FGF-23	miRNA 21 miRNA 23a miRNA 24 miRNA 25 miRNA 100 miRNA 125b miRNA 133a miRNA 148a miRNA 214 miRNA 503
		Wnt signaling molecules: Dkk-1, sFRP sphingosine-1-phosphate (S1P)		