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Review

Bone turnover markers in serum and urine as diagnostic, prognostic and monitoring biomarkers of bone metastasis

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ABSTRACT

Bone metastases are characterized by increased osteoblastic and/or osteolytic processes depending on the tumor type. The altogether destructive effect of metastasis formation promoted by increased metabolic activity raises the release of components from the osseous metabolism into the blood stream. These components are either enzymes directly involved in the alteration processes, metabolites/proteins that develop during this or bone matrix proteins released during this. These biomarkers are categorized in relation to their involvement in the bone formation or resorption as bone formation and resorption markers. Based on a PubMed literature search, a critical appraisal of the various biomarkers for diagnostic, prognostic, and monitoring purposes is given for patients with skeletal metastases caused by breast, prostate, lung, or renal cell carcinomas.

Contents

Abbreviations: BAP, bone-specific alkaline phosphatase; BCE, bone collagen equivalents; BSP, bone sialoprotein; CLIA, chemoluminescence immunoassay; CREA, urinary creatinine; CTX, carboxy-terminal cross-linking telopeptide of type I collagen; DPD, deoxypyridinoline (lysylpyridinoline); DKK-1, Dickkopf-1; ECLIA, electrochemoluminescence immunoassay; ICTP, carboxy-terminal cross-linking telopeptide of type I collagen, generated by MMPs; NTX, N-terminal cross-linking telopeptide of type I collagen; OC, osteocalcin; OPG, osteoprotegerin; OPN, osteopontin; PICP, carboxy-terminal propeptide of type I procollagen; PINP, amino-terminal propeptide of type I procollagen; PYD, pyridinoline (lysylhydroxypyridinoline); RANKL, receptor activator of NF-kappaB ligand; RIA, radioimmunoassay; ROC, receiver-operating characteristics; TRAP5b, tartrat-resistant acid phosphatase type 5b

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1. Introduction

Metastases in the bone lead to defective hemostasis that physiologically exists in the balance between the formation of new and the resorption of old osseous segments by osteoblasts and osteoclasts, respectively [1]. The morbidity of patients with advanced cancer is essentially caused by the occurrence of bone metastases [2]. Most patients with bone metastases experience complications, the so-called skeletal-related events that summarize hypercalcemia, severe bone pain, pathological bone fractures, spinal cord compression, and surgery to bone because of bone instability. Thus, an early diagnosis and specific prediction of patients at risk of skeletal complications is of great interest to improve the clinical management of these patients not only in reducing these complications but also increasing overall survival by a bone-targeted therapy [3–5].

The histomorphology of bone metastases showed metastasis formation in form of increased osteolytic and/or osteoblastic processes depending on the tumor type. During the metastatic process, components from the osseous metabolism are increasingly released into the blood stream, promoted by increased metabolic activity and the altogether destructive effect of metastasis formation [6]. These components are either enzymes directly involved in the alteration processes, metabolites that develop during this or bone matrix proteins released during this [7]. These biomarkers are generally categorized into bone formation and resorption markers based on their reflection of osseous formation or resorption [8]. Their determination in the serum and/or urine provides the opportunity to use them for questions in diagnostics, evaluation of the prognosis and treatment of patients with skeletal metastases [9]. In this respect, the aim of this review is focused on the appraisal of the current usefulness of these markers in practice rather than discuss the molecular processes in detail. There is the intention to sensitize basic scientists for the future-oriented task to translate novel molecular findings in bone metastatic processes into improved clinical tools.

2. Bone formation and resorption markers and their determinations in serum and urine

2.1. Analytical methods and variability of bone markers

A number of bone markers can be determined using commercial tests in the meantime. In regards to the method, enzyme immunological procedures have established themselves over radioimmunoassays. These tests are increasingly adapted using laboratory machines that achieve higher analytical reliability during the determination as compared to manual ELISA methods [10,11]. Serum/plasma is recommended as test material over urine for reasons of better practicability and lower inter- and intra-individual variability [12,13]. Sample collection and handling are essential pre-analytical factors that could differently affect the stability of the different bone markers [14,15]. As the biological variability of bone markers essentially influences their clinical interpretation, the influencing factors of this variability have to be regarded [16,17]. Age, sex, or menopausal status are uncontrollable factors and should be considered in form of different reference intervals (see also Table 1). In contrast, controllable factors of the biological variability and the pre-analytic phase (e.g., diurnal, seasonal, menstrual, diet, and exercise effects; kind of samples, storage) could be accounted to a great extent by a standardized sampling process (time and conditions of sampling, subsequent processing of samples) [15,16].

Table 1 shows test systems with their orientating reference ranges for the most commonly used markers [18–20]. This assay overview is necessary since bibliographical information on the test systems and their manufacturers to date are often no longer applicable due to company takeovers. The significant problem of method comparability of bone marker determinations is made clear by the sometimes significant differences in the reference intervals and the different reference systems used for the same markers.

Sex- and age-dependent reference intervals that were calculated based on determinations using a numerically sufficient reference population in consideration of recognized statistical procedures have been rare to date [18,21]. This problem was recently discussed in detail for the three bone markers bone-specific alkaline phosphatase (BAP), amino-terminal propeptide of type I procollagen (PINP), and carboxy-terminal cross-linking telopeptide of type I collagen (CTX) [18]. The comparability of the results of bone marker determinations between laboratories is also unsatisfactory even if identical methods were used [10,22]. This lack of comparability of bone marker determinations has already been recognized in osteoporosis diagnostics [23–25]. The goal is to harmonize the methods and use joint standards for the analyte measurements, but also include pre- and post-analytical aspects [15,26]. First efforts have already been made in this regard for skeletal metastasis diagnostics [27].

2.2. Biomarkers of bone formation

2.2.1. Bone-specific alkaline phosphatase

Bone-specific **a**lkaline **p**hosphatase (BAP) promotes bone mineralization. The enzyme is secreted by the osteoblasts. Increased concentration in the serum is primarily considered a sign of primarily increased osteoblast activity or secondarily as a corrective reaction as a result of increased bone resorption [7]. Preceding chemical and electrophoretic methods as selective approaches to discriminate BAP from the liver and intestinal alkaline phosphatase isoenzymes have been replaced by immunological methods [28]. There are two available methods which measure either the protein mass (e.g., Access Ostase) or enzyme activity (e.g., Ostase BAP EIA) as manual and automated test procedures (Table 1). Both methods provide highly comparable results [29].

2.2.2. Osteocalcin

Osteocalcin (OC) is the dominant non-collagenous protein of the bone matrix [30]. This bone-specific protein is synthesized by osteoblasts depending on vitamins K and D3. Various osteocalcin fragments