

# Role of the Clinical Laboratory in the Assessment of Metabolic Musculoskeletal Diseases

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Clinicians rely on laboratory results daily to treat and monitor patients. In fact, biomarkers are inexpensive, noninvasive, and reliable tools that provide objective information on pathophysiological mechanisms, aid in the diagnosis of diseases, allow for the evaluation of the therapeutic response to pharmacological treatment and the monitoring of side effects. Occasionally, they can also serve as substitute endpoints in clinical trials. As a result, bone turnover markers have been widely utilised in osteoporosis patients, particularly for monitoring treatment adherence. However, such biomarkers have not always been free of criticism, and their use and interpretation in clinical practice is contingent upon a thorough understanding of the various conditions that could potentially lead to ambiguous results. Therefore, a close relationship between clinicians and laboratory medicine specialists is required for optimal use of these markers in clinical practice. The collaboration between the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) is a success story for the best care of patients that began more than a decade ago with seminal papers that paved the way for a better utilisation of bone markers in clinical practice [1–8]. In this special issue of *Calcified Tissue International*, we have solicited authoritative reviews from members of the IOF, IFCC, and the European Society for Clinical and Economical aspects of Osteoporosis and Musculoskeletal Diseases (ESCEO) on various and significant contributions of laboratory medicine to the field of osteoporosis and musculoskeletal diseases. The special issue begins with a review by Diemar, Jørgensen and collaborators [9] on the circadian rhythm of bone biomarkers, an essential but occasionally

overlooked aspect of the preanalytical phase. Based on a comprehensive literature research, they concluded that this rhythm is present in several bone markers, including PINP,  $\beta$ -CTX, osteocalcin, bone alkaline phosphatase, and PTH. Thus, the authors suggested that blood should be drawn in the morning, preferably from fasting patients, and that if measurements are to be repeated, they should be taken at the same time of day and under the same conditions. In the next article, Samuel Vasikaran and other members of the IFCC Committee on Bone Metabolism (IFCC C-BM) [10] presented novel and crucial considerations regarding the clinical application of bone turnover markers (BTMs) in osteoporosis. If they confirmed the importance of  $\beta$ -CTX and PINP for monitoring therapy of osteoporosis, they highlighted the potential importance of bone alkaline phosphatase and TRACP-5b, especially (but not exclusively) in patients with chronic kidney diseases. In addition, they emphasised the importance of standardisation or harmonisation of commercial assays for optimal utilisation of these relevant biomarkers. Markus Herrmann and his colleagues have emphasised the significance of good analytical tools such as mass spectrometry coupled with liquid chromatography (LCMS/MS) and the emerging significance of 24,25-dihydroxy vitamin D [11] and the vitamin D metabolite ratio (VMR) to define vitamin D deficiency [12, 13]. Vitamins D and K are known to play an important role in musculoskeletal health, despite the fact that different studies have given inconsistent results, as far as vitamin supplementation in vitamin D or K replete individuals. However, these discrepancies may be partly attributable to the methods used to quantify the biomarkers, the selection of the biomarker of interest, or the method used to assess the deficiency.. Similarly, a group of ESCEO experts has provided a consensus report on the list of biochemical markers of musculoskeletal status that should be assessed in all Phase II and Phase III clinical trials of drugs intended for the management of sarcopenia [14]. It would be incorrect to assume that BTMs are only utilised in elderly individuals. Indeed, if they remain most of the time research tools in paediatrics, bone disorders like renal osteodystrophy or glucocorticoid-induced osteoporosis can also occur in children and may necessitate BTMs in their management. However, laboratory medicine in children presents unique challenges. These issues are presented by Aurélie Ladang, Frank Rauch, Edgard Delvin and Etienne Cavalier [15]. In the following article of this issue, Konstantinos Makris has summarised the most significant findings regarding the clinical and analytical aspects of alkaline phosphatases [16]. Alkaline phosphatases are likely one of the most

frequently utilised biomarkers in children. Even though this group of enzymes has been known for decades, not all of its secrets have been revealed.

Research on bone and muscle biomarkers is intensive, and a number of biomarkers have emerged in recent years. Among them, sclerostin and Dickkopf-related protein 1 (DKK1) are particularly intriguing because they regulate bone metabolism via the Wnt/ $\beta$ -catenin signalling pathway. Aylin Sepinci Dincel and Niklas Rye Jørgensen have reviewed the clinical utility of these two emerging biomarkers and have provided relevant information on the preanalytical and analytical phases as well as on the reference ranges of both biomarkers [17]. Annemieke Heijboer and Etienne Cavalier have compiled the most recent findings regarding on the the analytical measurement of FGF23 and its clinical indications [18]. Indeed, Fibroblast Growth Factor 23 (FGF23) is as a major phosphaturic hormone that plays a central role in a large variety of diseases. Last but not least, Giovanni Lippi and Edgard Delvin have written an exciting and highly informative article on micro-RNAs and on their association with bone mineral density, fractures and osteoporosis, which paves the way for new research avenues [19].

All of the contributors to this Special Issue of *Calcified Tissue International* have endeavoured to emphasise the significance of the analytical and preanalytical phases for optimal utilisation of current and emerging biomarkers of bone turnover and musculoskeletal diseases. I sincerely hope that these ten articles will be useful not only for laboratory medicine specialists, but also for the clinicians who treat patients with various bone and musculoskeletal disorders on a daily basis.

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