Calcified Tissue International (2023) 112:123–125
https://doi.org/10.1007/s00223-022-01045-0

EDITORIAL

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

Etienne Cavalier[1,2,3]

Received: 7 November 2022 / Accepted: 16 November 2022 / Published online: 27 December 2022

Clinicians rely on laboratory results daily to treat and monitor patients. In fact, biomarkers are inexpensive, non-invasive, 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, β-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 β-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

✉ Etienne Cavalier
Etienne.cavalier@chuliege.be

[1] Department of Clinical Chemistry, University of Liege, CIRM, CHU de Liège, Liège, Belgium

[2] The International Federation of Clinical Chemistry and Laboratory Medicine, IFCC, Milan, Italy

[3] The International Osteoporosis Foundation, IOF, Nyon, Switzerland

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/β-cathenin 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.

Acknowledgements This Special edition is a joint contribution of the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)

References

1. Vasikaran S, Eastell R, Bruyère O et al (2011) Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int 22:391–420. https://doi.org/10.1007/s00198-010-1501-1
2. Vasikaran S, Cooper C, Eastell R et al (2011) International osteoporosis foundation and international federation of clinical chemistry and laboratory medicine position on bone marker standards in osteoporosis. Clin Chem Lab Med 49:1271–1274. https://doi.org/10.1515/CCLM.2011.602
3. Morris HA, Eastell R, Jorgensen NR et al (2017) Clinical usefulness of bone turnover marker concentrations in osteoporosis. Clin Chim Acta 467:34–41
4. Cavalier E, Eastell R, Jørgensen NR et al (2019) A multicenter study to evaluate harmonization of assays for N-terminal propeptide of type I procollagen (P1NP): a report from the IFCC-IOF joint committee for bone metabolism. Clin Chem Lab Med 25:1546–1555
5. Vasikaran SD, Bhattoa HP, Eastell R et al (2020) Harmonization of commercial assays for PINP; the way forward. Osteoporos Int. https://doi.org/10.1007/s00198-020-05310-6
6. Cavalier E, Lukas P, Bottani M et al (2020) European biological variation study (EuBIVAS): within- and between-subject biological variation estimates of β-isomerized C-terminal telopeptide of type I collagen (β-CTX), N-terminal propeptide of type I collagen (PINP), osteocalcin, intact fibroblast growth factor 23 and uncarboxylated-unphosphorylated matrix-Gla protein—a cooperation between the EFLM working group on biological variation and the international osteoporosis foundation-international federation of clinical chemistry committee on bone metabolism. Osteoporos Int. https://doi.org/10.1007/s00198-020-05362-8
7. Bhattoa HP, Cavalier E, Eastell R et al (2021) Analytical considerations and plans to standardize or harmonize assays for the reference bone turnover markers PINP and beta-CTX in blood. Clin Chim Acta 515:16–20. https://doi.org/10.1016/j.cca.2020.12.023
8. Cavalier E, Eastell R, Jørgensen NR et al (2021) A multicenter study to evaluate harmonization of assays for C-Terminal telopeptides of type I collagen (ß-CTX): a report from the IFCC-IOF committee for bone metabolism (C-BM). Calcif Tissue Int 108:785–797
9. Diemar SS, Dahl SS, West AS et al (2022) A systematic review of the circadian rhythm of bone markers in blood. Calcif Tissue Int. https://doi.org/10.1007/s00223-022-00965-1
10. Vasikaran SD, Miura M, Pikner R et al (2021) Practical considerations for the clinical application of bone turnover markers in osteoporosis. Calcif Tissue Int. https://doi.org/10.1007/s00223-021-00930-4
11. Cavalier E, Huyghebaert L, Rousselle O et al (2019) Simultaneous measurement of 25(OH)-vitamin D and 24,25(OH)2-vitamin D to define cut-offs for CYP24A1 mutation and vitamin D deficiency in a population of 1200 young subjects. Clin Chem Lab Med 58:197–201. https://doi.org/10.1515/cclm-2019-0996
12 Alonso N, Zelzer S, Eibinger G, Herrmann M (2022) Vitamin D metabolites: analytical challenges and clinical relevance. Calcif Tissue Int. https://doi.org/10.1007/s00223-022-00961-5
13 Alonso N, Meinitzer A, Fritz-Petrin E et al (2022) Role of vitamin K in bone and muscle metabolism. Calcif Tissue Int. https://doi.org/10.1007/s00223-022-00955-3
14. Ladang A, Beaudart C, Reginster J-Y, et al (2022) Biochemical markers of musculoskeletal health and aging to be assessed in clinical trials of drugs aiming at the treatment of sarcopenia. Calcif Tissue Int. https://doi.org/10.1007/s00223-022-01054-z
15. Ladang A, Rauch F, Delvin E, Cavalier E (2022) Bone turnover markers in children: from laboratory challenges to clinical interpretation. Calcif Tissue Int. https://doi.org/10.1007/s00223-022-00964-2

16. Makris K, Mousa C, Cavalier E (2022) Alkaline phosphatases: biochemistry, functions and measurement. Calcif Tissue Int. https://doi.org/10.1007/s00223-022-01048-x
17 Dincel AS, Jørgensen NR (2022) New emerging biomarkers for bone disease: sclerostin and Dickkopf-1 (DKK1). Calcif Tissue Int. https://doi.org/10.1007/s00223-022-01020-9
18 Heijboer AC, Cavalier E (2022) The measurement and interpretation of fibroblast growth factor 23 (FGF23) concentrations. Calcif Tissue Int. https://doi.org/10.1007/s00223-022-00987-9
19. Lombardi G, Delvin E (2022) Micro-RNA: A future approach to personalized diagnosis of bone diseases. Calcif Tissue Int. https://doi.org/10.1007/s00223-022-00959-z