



Bone metabolism—beyond calcium and phosphate homeostasis

Bone has long been seen as a rather static organ that maintains human postural stability, mediates movements via the skeletal muscles and hosts haematopoiesis in the bone niche. In addition, the skeleton is known to protect important organs, such as brain, gut, liver and others. In recent years huge research efforts have revealed that this neglected organ has many other essential functions in the body. For example, it appears that bone has a regulatory role in energy metabolism, fertility, brain development, and cognition (1). The cross-talk between bone and various other organs is mediated through bone derived molecules with endocrine properties, such as osteocalcin or sclerostin (1-4). As a consequence, bone is increasingly considered an endocrine gland that produces several hormones. It has also been shown that bone is a dynamic organ that undergoes constant remodelling. The discovery of important regulatory proteins, such as RANKL (receptor activator of nuclear factor κ B ligand), OPG (osteoprotegerin) or sclerostin led to a new understanding of osteoblasto- and osteoclastogenesis (5,6). Specific aspects of bone metabolism and homeostasis are increasingly recognized as key factors or crucial contributors to intersystemic diseases, such as diabetes, atherosclerosis and dementia (1-4).

Besides the discovery of new molecules and regulatory pathways substantial advances in the accurate measurement of bone-related biomarkers have been made. For example, PTH immunoassays continue to improve allowing an always more specific measurement of intact 1-84 PTH thus limiting spurious results (7). Another example is the measurement of 25-hydroxy vitamin D [25(OH)D], which is rapidly evolving. Mass spectrometry is increasingly used to accurately quantitate this analyte. In addition to the accurate determination of 25(OH)D, mass spectrometry allows the simultaneous quantification of related metabolites, such as 24,25-dihydroxy vitamin D [24,25(OH)₂D] and 1,25-dihydroxy vitamin D [1,25(OH)₂D], which has opened new possibilities in exploring the complex metabolism of vitamin D in several clinical situations. The ratio between the inactive precursor 25(OH)D and the most abundant catabolite 24,25(OH)₂D appears to provide an explanation for the conundrum of comparable bone mineral density and fracture risk in white and black Americans despite 40% lower 25(OH)D levels (8). In a series of review articles this focused issue of *Journal of Laboratory and Precision Medicine (JLPM)* addresses several of these novel clinical and analytical aspects.

Periodontitis is a common but often neglected example that illustrates the cross-talk between bone and other tissues, such as teeth, immune cells and the periodontium (9). The disease leads to teeth loss caused by an excess of bone resorption over bone formation. Chronic infection and inflammation of the gingiva activate immune-modulatory cells and trigger a type of osteo-immunological diseases. Typical bone-derived factors, such as RANKL and OPG are increased in the periodontium, stimulating osteoclastogenesis and bone resorption. In parallel, Wnt signalling decreases resulting in impaired osteoblast differentiation.

The continuous remodelling of bone requires a substantial amount of energy. Therefore, it is not surprising that bone is tightly linked to energy metabolism. For example, diabetic individuals harbour an up to twelvefold higher fracture risk than individuals with normal glucose homeostasis. In addition, diabetics show a general tendency for delayed fracture and wound healing. Obermayer-Pietsch *et al.* (10) describe the sequelae of “diabetoporosity”, the combination of diabetes and osteoporosis. Their article provides an overview about diagnostic approaches to identify diabetic patients at increased risk of fractures. Furthermore, they discuss, the contribution of various treatment options to fracture risk and the potential consequences for prevention and medication.

In geriatric patients, osteoporosis, sarcopenia (loss of muscle mass and strength) and changes in fat distribution as well as function often coincide. The cross-talk between bone, muscle and fat explains the concurrent development of these conditions. Our improved understanding of these relationships has led to the definition of osteosarcopenia as novel geriatric disease. Al Saedi *et al.* (11) discuss local lipotoxicity induced by intramuscular (even intramyocellular) and bone marrow fat. They also describe new diagnostic aspects of osteosarcopenia, such as the identification and quantification of tissue-derived fat and lipotoxic adipokines. At present, the function of many adipokines, myokines and bone-derived compounds is insufficiently understood. For example, sclerostin was initially identified as a regulator of bone remodelling. However, recent research suggests that it is also involved in the pathogenesis of pulmonary hypertension via BMP and WNT-related pathways. In another review article Biasin *et al.* discuss the potential role of Wnt-signalling lung vasculature (12). This knowledge may

open new diagnostic and therapeutic options for patients with primary or secondary pulmonary hypertension.

Gut microbes, often summarized under the term microbiome, also interact with bone metabolism and contribute to intersystemic diseases. In this issue of *JLPM* Medina-Gomez (13) review existing knowledge regarding the microbiome and its relations with bone metabolism. Animal models and clinical studies suggest that microbiota and their metabolism influence bone formation and resorption via mechanisms that involve the sympathetic nervous system and other factors. MicroRNAs (miRNAs), small non-coding ribonucleic acid (RNA) molecules, have also been shown to modulate bone metabolism through complex interactions with DNA transcription. Foessl *et al.* (14) review existing data on this topic. Distinct patterns of miRNAs seem to provide specific information on tissue and organ functions. This knowledge may trigger new diagnostic and therapeutic applications. However, more research is needed to elucidate their full diagnostic potential and to proof their therapeutic usefulness.

New insights in the analysis and interpretation of “established” biomarkers of bone and calcium metabolism are described by Cavalier (7) for parathyroid hormone (PTH) and Zelzer *et al.* for vitamin D (15). PTH is routinely measured by immunoassays, which aim to detect the active PTH 1-84 molecule. However, these assays can be interfered by various breakdown fragments that accumulate in various physiological and pathological conditions, such as renal failure. Although manufacturers continuously try to improve specificity the analytical performance of commercial PTH assays is still variable. Cavalier *et al.* review differences in major PTH assays, “new” forms of PTH such as Amino-PTH, oxidized and non-oxidized PTH and refer to the actual guidelines. In clinical practice PTH results need to be interpreted against the clinical background and the analytical performance of the assay used for determination. Patients with chronic kidney disease (CKD) or CKD bone mineral disorder (CKD-MBD) are particularly affected from interferences of breakdown fragments because they accumulate due to the impairment of renal function. In these patients the use of least significant change (LSC) or clinical targets is highly warranted. Immunoassays for 25(OH)D also suffer a variable analytical performance which limits comparability of results. Isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) is the gold standard for the measurement 25(OH)D. Although this technology is increasingly used by clinical laboratories methods vary substantially. Different extraction procedures, internal standards and liquid chromatography protocols are used. Zelzer *et al.* (8) provide a comprehensive overview about LC-MS/MS methods for the measurement of 25(OH)D and related metabolites.

In summary, this fascinating issue of *JLPM* provides insights in novel clinical and analytical aspects of bone with a special focus on intersystem diseases. The review articles on the following pages will help to create awareness for the interactions between bone and other organs these. Furthermore, they will provide an overview about the capabilities of novel and established biomarkers. It can be expected that future research will help to transfer this knowledge in clinical practice.

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Markus Herrmann



Barbara Obermayer-Pietsch

Barbara Obermayer-Pietsch, Prof, MD

*Endocrinology Lab Platform, Division of Endocrinology and Diabetology,
Department of Internal Medicine and Department of Gynaecology and Obstetrics,
Medical University Graz, Graz, Austria. (Email: Barbara.obermayer@medunigraz.at)*

Markus Herrmann, Prof, MD

*Clinical Institute for Medical and Chemical Laboratory Diagnostics,
Medical University of Graz, Graz, Austria. (Email: markus.herrmann@medunigraz.at)*

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