Kidney Medicine

Mineral, Bone, and Cardiovascular Disorders in CKD: The Case for a New Paradigm

Angela Yee-Moon Wang, Paul D. Miller, Hirotaka Komaba, Sandro Mazzaferro, Jordi Bover, Jonathan Himmelfarb, Charles J. Ferro, Pablo A. Urena-Torres, Mario Cozzolino, David W. Dempster, Tetsuo Shoji, Rukshana Shroff, Ziad A. Massy, and Michael Pazianas

Chronic kidney disease (CKD) profoundly affects both the cardiovascular (CV) and skeletal systems, with CV disease (CVD) being the leading cause of death in patients with advanced CKD (stages 4-5) and dialysis patients.[1] However, in the early years of CKD-mineral bone disorder (CKD-MBD) research and treatment, and for decades thereafter, attention was directed almost entirely toward bone, whereas sustained, systematic interest in mineral disorder-related CV complications emerged only relatively recently. The focus on bone began once parathyroid hormone (PTH) could first be measured, showing its elevation in CKD, and was further established in the early 1970s with the discovery of the active vitamin D metabolite $1,25(OH)_2D$. This shaped both scientific interest and therapeutic strategies for decades and was amplified further by the characterization of PTH as a uremic toxin. Despite intense investigations, however, the anticipated improvements in routine clinical practice have largely failed to materialize. Moreover, although Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have undoubtedly improved patient management, they have achieved limited success in driving research breakthroughs that could further advance care.

The discovery of Klotho, FGF-23, and sclerostin, key hormones in mineral homeostasis, bone integrity, and CV health, has had limited clinical impact. This is not because of a lack of investigative effort, but rather to the extreme complexity of the CKD-MBD pathophysiology, and, potentially, to the way we apply the longstanding PTH-centric model. The model itself is not inherently flawed, but its components are often weighed unevenly. For example, PTH is regarded more as a toxin, whereas $1,25(OH)_2D$ is viewed as a remedy.

These factors, collectively with the negative results of several randomized clinical trials targeting CKD-MBD management in CKD patients and patients receiving dialysis, have gradually reduced industry interest in sponsoring large outcomes trials in CKD-MBD.[2] Large trials take years to conduct and involve huge funding support; however, they may not yield expected outcome and return. It has also diminished the nephrology community's attention to CKD-related bone disease. The trend is evident in the small number of related abstracts submitted to major nephrology conferences and the proportional time devoted to the topic during these meetings in the recent few years. This loss of engagement is evident in particular for osteoporosis, as specifically highlighted in a *Lancet Diabetes & Endocrinology* editorial that noted that "nephrologists have seldom been engaged in treatment decisions for osteoporosis."[3] Only 2.3% of patients undergoing dialysis in the study by Bird et al[4] received treatment for osteoporosis from a specialist in nephrology, and the researchers concluded that nephrologists should be more directly involved in managing osteoporosis in patients with CKD, particularly in those at high risk of severe hypocalcemia (eg, denosumab).

If bones and minerals have suffered neglect in recent years, the CV side of mineral disorder-related CKD complications has equally struggled to remain an area of active interest. Despite growing interest in the CV–kidney–metabolic syndrome, vascular and valvular calcification remains relatively unexplored in nephrology. In 2006, KDIGO introduced the term CKD-MBD in an effort to provide a unified nomenclature and framework for mineral, bone, and associated CV complications of CKD.[5] Although the intention was inclusive, the label itself does not explicitly convey the CV content. Members of the original KDIGO group recognized this limitation but nonetheless proceeded with the CKD-MBD abbreviation, largely because they were unable to identify an alternative equally concise and likely to gain acceptance. Osteoporosis was also not incorporated, despite being highly prevalent among the older CKD population, which constitutes the majority of patients.

This is the moment for nephrology and relevant stakeholders to act decisively and bring these high-priority areas back to prominence. One important step would be to revise the nomenclature itself so that it explicitly incorporates the cardiovascular dimension. The term CKD-Mineral, Bone, and Cardiovascular Disorders (CKD-MBCVD) more accurately reflects the pathophysiology of CKD, in which CVD is not an external or secondary complication, but an intrinsic component of the syndrome.

Within this integrated framework, the commonly used term "CKD-associated cardiovascular disease" becomes conceptually redundant rather than contradictory.[6] CVD in CKD is not merely associated with mineral and bone disorders; it evolves in parallel and shares common mechanistic drivers, including disturbances in calcium–phosphate homeostasis, bone turnover, and endocrine feedback loops. Similar reasoning has already been applied to other manifestations of CKD-MBD: we do not refer to "CKD-associated hyperparathyroidism" or "CKD-associated adynamic bone disease" because these

conditions are understood to be inherent features of the syndrome. Extending this logic to CVD improves conceptual clarity and avoids artificial separation of interdependent processes.

Osteoporosis should likewise be incorporated within the renal bone disease spectrum, eliminating the current distinction between "CKD-induced osteoporosis" and preexisting osteoporosis in patients with CKD. Given the advanced age and multimorbidity of most CKD populations, osteoporosis and CVD should be regarded as integral components of CKD-MBCVD rather than parallel, loosely connected entities.

Nomenclature reform is only the first step. Equally important is rethinking the conceptual approach to mineral and bone disorder in CKD. The field urgently needs a new research direction that could achieve breakthroughs and transform clinical practice. At the level of diagnosis, a major challenge in CKD-MBD is distinguishing biomarkers that reflect adaptive, corrective responses within tightly regulated feedback loops from those that signify maladaptive pathology. Although biomarkers—including selected markers of bone formation and resorption that are unaffected by kidney function—may provide useful descriptive information, their clinical interpretation is likely to remain limited until the underlying pathophysiology of CKD-MBD is better defined using integrative, mechanism-based approaches.

The longstanding PTH-centric model remains sound, yet its translation into practice has fallen short. We often suppress PTH too early (increasing the risk for adynamic bone) or attempt to lower PTH once secondary hyperparathyroidism has been established. In addition, our near-exclusive reliance on $1,25(OH)_2D$ as the primary therapeutic strategy has not helped because it further diverted attention from potentially more effective targets. Clinical practice has frequently over relied on $1,25(OH)_2D$ and analogs largely because they are readily manipulated pharmacologically, whereas precise modulation of PTH or FGF-23 remains more challenging. However, it is the delayed PTH response to phosphate retention, rather than the vitamin D or other bone hormones, that appears to be the key link affecting calcium–phosphate homeostasis and allowing skeletal and CV complications.[7]

In CKD, elevations in PTH reflect secondary hyperparathyroidism and represent a compensatory attempt to restore calcium–phosphate balance rather than a primary pathogenic process, in contrast to primary hyperparathyroidism. A similar interpretation applies to other components of the regulatory network, including FGF-23 and changes in $1,25(OH)_2D$, which initially function as corrective responses to phosphate retention but may become maladaptive when chronically or excessively activated.

Potential interventions may therefore include strategies aimed at preserving endogenous parathyroid responsiveness to phosphate retention by preventing early functional suppression of PTH signaling and maintaining its normal dynamic, adaptive secretion. Modulation of upstream regulators of PTH secretion in this context refers primarily to interventions that reduce phosphate-driven, FGF-23–dominant compensation and restore effective renal responsiveness to PTH, thereby shifting phosphate regulation back toward physiological PTH-mediated control.

Within this framework, intermittent PTH administration, designed to mimic physiological signaling, represents a rational strategy to restore early phosphate handling through the kidney and, subsequently, re-engage skeletal phosphate buffering. By reinstating a timely PTH response to phosphate retention, such an approach could reduce the need for sustained elevations of FGF-23—an initially adaptive but ultimately maladaptive response—and thereby preserve systemic calcium–phosphate homeostasis, with parallel benefits for both skeletal integrity and cardiovascular health.

These changes, ie, updating nomenclature, reframing disease components (especially, incorporating osteoporosis as part of the renal bone disease spectrum), and elevating CVD to a priority, are essential steps. They could provide a common platform for nephrologists, scientists, bone specialists, cardiologists, patients, and allied health professionals to work more closely together, fostering collaborations that advance both research and clinical care. The inclusion of CVD in the 2012 KDIGO guidelines marked the first formal recognition, surprisingly late given the severity of this complication.[8] Since then, however, clinical demands have outpaced available strategies, and the gap between needs and actions has only widened. Although treatment of established CVD remains important, continuing to focus primarily on its consequences represents a shortcoming; instead, prevention must take center stage, as strongly emphasized by the Lancet Commission.[9] A recent study in children with CKD showed that nearly 80% had more than 3 modifiable risk factors for CVD, and 75% had subclinical CV damage even before kidney replacement therapy onset.[10] Children are an ideal cohort to study the earliest changes of CVD in relation to derangements in mineral metabolism, because they lack pre-existing CVD, traditional Framingham risk factors such as diabetes or hypercholesterolemia, and are not smokers.

The definitive measure of both short and long-term success, however, will be our ability to introduce novel conceptual frameworks for understanding the pathophysiology of disordered calcium–phosphate homeostasis and the development of various bone and CV complications associated with CKD, with the potential to translate directly into better detection and diagnosis, better prevention, more effective treatment strategies, and improved outcomes for all patients with CKD. Exploring the critical role of a delayed PTH response could represent one such pivotal shift.[8] Taken together, these considerations underscore both the urgency and the considerable gap we must close.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Angela Yee-Moon Wang, MD, PhD, Paul D. Miller, MD, Hirotaka Komaba, MD, PhD, Sandro Mazzaferro, MD, Jordi Bover, MD, PhD, Jonathan Himmelfarb, MD, Charles J. Ferro, MD, Pablo A. Urena-Torres, MD, PhD, Mario Cozzolino, MD, PhD, David W. Dempster, PhD, Tetsuo Shoji, MD, PhD, Rukshana Shroff, MD, PhD, Ziad A. Massy, MD, PhD, and Michael Pazianas, MD

Authors' Affiliations: Department of Renal Medicine, Singapore General Hospital, Singapore (AWYM); Duke-National University of Singapore, Singapore (AWYM); University of Colorado Health Sciences Center, Denver, CO (PDM); Colorado Center for Bone Health, Lakewood, CO (PDM); Department of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan (HK); Department of Translation and Precision Medicine, Sapienza University of Rome, Rome, Italy (SM); Department of Nephrology, University Hospital Germans Trias I Pujol, REMAR-IGTP and RICORS2040 Groups, Badalona (Barcelona), Catalonia, Spain (JB); Barbara T. Murphy Division of Nephrology, Center for Kidney Disease Innovation (MS-CKDi), Samuel Bronfman Department of Medicine, Icahn School of Medicine at Mount Sinai, New York City, NY (JH); Department of Renal Medicine, University Hospitals Birmingham and Institute of Cardiovascular Sciences, University of Birmingham, UK (CF); Department of Nephrology and Dialysis, AURA Nord Saint-Ouen, Saint-Ouen, France (PAU-T); Department of Renal Physiology, Necker Hospital, University of Paris Descartes, Paris, France (PAU-T); Renal Division, Department of Health Sciences, University of Milan, Milan, Italy (MC); Vagelos College of Physicians and Surgeons of Columbia University, New York City, NY (DWD); Clinical Research Center, Inoue Hospital, Suita, Osaka, Japan (TS); Department of Metabolism, Endocrinology and Molecular Medicine, Osaka Metropolitan University Graduate School of Medicine, Osaka, Osaka, Japan (TS); Paediatric Nephrology Unit, University College London Great Ormond Street Hospital and Institute of Child Health, London, UK (RS); Inserm Unit 1018, Team 5, CESP, Hôpital Paul Brousse, Paris-Saclay University (UPS) and Versailles Saint-Quentin-en-Yvelines University (UVSQ), Villejuif, France (ZAM); Department of Nephrology, Ambroise Paré University Hospital, APHP, Boulogne-Billancourt/Paris, France (ZAM); and Institute for Translational Medicine and Pharmacology, Icahn Sinai School of Medicine at Mount Sinai, New York, NY (MP).

Address for Correspondence: Michael Pazianas, MD, Icahn Sinai School of Medicine at Mount Sinai, 1 Gustave L. Levy PI, New York, NY 10029. Email: Michael.Pazianas@mssm.edu

Support: None.

Financial Disclosure: Dr Wang has received speaker honoraria from Astra Zeneca, Fresenius Kabi, and Bayer AG. She has served on the advisory board for Fresenius Kabi and as a steering member for a phase 3 global clinical trial sponsored by CSL Behring. Dr Massy reports grants for CKD-REIN and other research projects from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp & Dohme-Chibret, Sanofi-Genzyme, Lilly, Otsuka, AstraZeneca, Vifor, and the French government, as well as fees and grants to charities from AstraZeneca, NovoNordisk, and Boehringer Ingelheim. Dr Dempster reports consultancy, grant support, and speaker fees from Amgen, Inc and Radius Health. Dr Shoji has received lecture fees from Kowa, Ono Pharmaceutical, Kyowa Kirin, Kissei, Sanwa Kagaku, and Vantive. Dr Komaba has received personal fees from Kissei Pharmaceutical, Kyowa Kirin, Ono Pharmaceutical, and Sanwa Kagaku Kenkyusho and grants from Kyowa Kirin. The other authors have nothing to disclose.

Peer Review: Received October 27, 2025. Accepted after editorial review by the Editor-in-Chief January 12, 2026.

REFERENCES

1. Thompson S, James M, Wiebe N, et al. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol*. 2015;26(10):2504-2511.
2. Nataatmadja M, Cho Y, Fahim M, Johnson DW. Recent clinical trials of pharmacologic cardiovascular interventions in patients with chronic kidney disease: an update. *Rev Recent Clin Trials*. 2016;11(1):12-32.
3. Covic A, Apetrii M. Denosumab in the treatment of osteoporosis associated with chronic kidney disease. *Lancet Diabetes Endocrinol*. 2024;12(4):225-227.
4. Bird ST, Smith ER, Gelperin K, et al. Severe hypocalcemia with denosumab among older female dialysis-dependent patients. *JAMA*. 2024;331(6):491-499.
5. Moe S, Drüeke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2006;69(11):1945-1953.
6. Valdivielso JM, Rodríguez-Puyol D, Pascual J, et al. Atherosclerosis in chronic kidney disease: more, less, or just different? *Arterioscler Thromb Vasc Biol*. 2019;39(10):1938-1966.
7. Pazianas M, Miller PD. The CKD-MBD syndrome: hysteresis in PTH involvement and PTH administration for its management. *J Bone Miner Res*. 2020;35(12):2313-2317.
8. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1-150.
9. Zaman S, Wasfy JH, Kapil V, et al. The Lancet Commission on rethinking coronary artery disease: moving from ischaemia to atheroma. *Lancet*. 2025;405:1264-1312.
10. Khandelwal P, Hofstetter J, Azukaitis K, et al. Changes in the cardiovascular risk profile in children approaching kidney replacement therapy. *EClinicalMedicine*. 2024;74:102708.