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Immune-metabolic crosstalk in chronic kidney disease-mineral and bone disorder; uremic toxins, inflammation, and bone-vascular axis dysregulation

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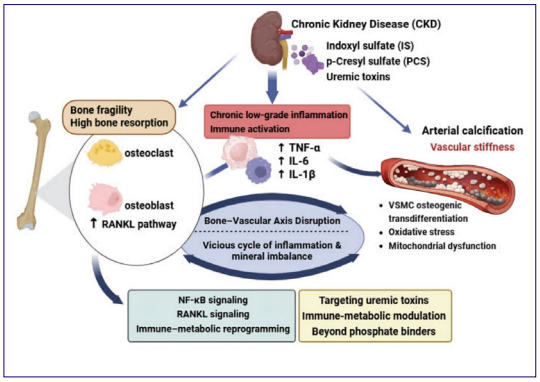
ABSTRACT



Chronic kidney disease-mineral and bone disorder (CKD-MBD) represents a complex systemic syndrome linking mineral metabolism abnormalities with extra-skeletal calcification and profound bone fragility. Whilst traditionally viewed through the lens of hormonal dysregulation involving parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23), emerging evidence highlights the pivotal role of immune-metabolic crosstalk in driving pathology. This overview considers how accumulated uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, act as the potent inflammatory mediators that critically and directly disrupt the bone-vascular axis. These toxins trigger chronic low-grade inflammation by activating innate and adaptive immune cells, including macrophages and T-lymphocytes, which subsequently alter osteoblast and osteoclast function through pro-inflammatory cytokine release. Concurrently, metabolic disturbances characterized by oxidative stress and mitochondrial dysfunction exacerbate vascular smooth muscle cell (VSMC) transdifferentiation into osteogenic phenotypes, directly promoting arterial calcification. Then, the interplay between immune activation and metabolic reprogramming creates a vicious cycle where accelerated bone resorption releases minerals that deposit in the vasculature, further worsening cardiovascular outcomes. Meanwhile, the distinction between renal bone disease and vascular calcification blurs, unified by shared inflammatory pathways and metabolic derangements involving NF-κB signaling and RANKL pathways. Identification of these mechanistic links is necessary for developing novel therapeutic strategies beyond conventional phosphate binders. Targeting specific uremic toxins or modulating immune-metabolic signaling pathways offers highly significant promise. Finally, addressing the inflammatory milieu induced by uremia may mitigate the high cardiovascular mortality associated with CKD-MBD, necessitating a paradigm shift towards integrated immune-metabolic interventions in contemporary nephrology practice to improve overall patient survival and reduce fracture risk significantly.

Review

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Implication for health policy/practice/research/medical education:
Chronic kidney disease-mineral and bone disorder (CKD-MBD) represents a systemic syndrome linking mineral metabolism with vascular calcification and bone fragility. Though traditional views emphasize hormonal dysregulation, emerging evidence highlights critical immune-metabolic crosstalk driving pathology. This review explores how uremic toxins, such as indoxyl sulfate, act as potent inflammatory mediators. These toxins activate immune cells, fostering chronic inflammation that disrupts osteoblast differentiation and vascular smooth muscle cell phenotypic switching. This condition promotes bone resorption while simultaneously driving vascular calcification, illustrating significant bone-vascular axis dysregulation. We examine molecular pathways connecting metabolic waste retention to immune activation and tissue mineralization. Identification of these interactions is imperative, since current therapies often fail to address underlying inflammatory drivers linked to mortality. Targeting uremic toxins or inflammatory cytokines may offer novel strategies to decouple bone loss from vascular stiffening. Finally, integrating immune-metabolic perspectives into CKD-MBD management could improve cardiovascular outcomes and bone health in this high-risk population.
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Introduction

Increasing numbers of cross-sectional studies in general populations and in patients with chronic kidney disease (CKD) or end-stage renal disease have reported associations between cardiovascular calcifications and bone disorders, such as osteoporosis, osteopenia, and varying bone activity (1). The mechanisms underlying this bone-cardiovascular axis and the biological connections between bone and arterial abnormalities suggest a bone-vascular cross-talk (1). The precise nature of these links is not fully understood but may arise from common factors affecting both bone remodeling and arterial calcification, compromised bone blood supply leading to arteriosclerosis of bone vessels and reduced perfusion, and/or direct actions of bone cells on vascular biology and structure (2). Inflammation and the accumulation of reactive oxygen species are the primary common pathways linking bone and arterial pathologies. (3) Uremic toxins play an important role in the bone-vascular axis in CKD, contributing to endothelial cell dysfunction, oxidative stress, and excessive inflammation (4). Patients with advanced CKD experience an accumulation of uremic toxins, a condition driven by reduced kidney function and altered gene expression that leads to increased metabolite generation. These toxins disrupt various biological functions of cells and organs, contributing to chronic inflammation and other adverse effects that can damage tissues (5). Uremic toxins have been implicated in significant changes to vascular smooth muscle cells and other alterations that result in vascular calcification and early vascular aging. Vascular calcification and early vascular ageing are prominent clinical features in CKD patients and contribute significantly to their high cardiovascular mortality (6). Uremic toxins are compounds that exert biological actions and are retained in patients with renal failure, although healthy kidneys would normally excrete them into the urine. Few retention solutes precisely fit the strict definition of uremic toxins (7). Uremic solutes can be categorized into small water-soluble compounds, small protein-bound compounds, and middle molecules. Most small water-soluble compounds are not highly toxic, and the toxic ones often exhibit kinetic behavior different from that of urea (8). The uremic solutes involved in inflammation and cardiovascular complications are frequently middle molecules and/or protein-bound compounds. Patients with chronic renal failure face a high risk of severe adverse outcomes, including progressive kidney function loss, cardiovascular disease, and premature death (9). Chronic kidney disease -mineral and bone disorder (CKD-MBD) is a clinical syndrome characterized by a systemic disorder of bone and mineral metabolism due to CKD, presenting with abnormalities in bone and mineral metabolism (10). Alterations in calcium and phosphate metabolism, commonly observed in secondary hyperparathyroidism of uremia, particularly in patients undergoing maintenance hemodialysis, contribute to ectopic calcification, cardiovascular disease, and an increased risk of mortality (11). This overview talks on the immune-metabolic crosstalk in CKD-MBD by considering uremic toxins, inflammation, and bone-vascular axis dysregulation.

Search strategy

For this review, we performed a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy employed a variety of relevant keywords, such as 'secondary hyperparathyroidism', 'chronic kidney disease', 'parathyroid hormone', 'uremia', 'fibroblast growth factor-23', 'vascular smooth muscle cell', 'end-stage renal disease', 'CKD-MBD' and 'vascular calcification'.

Mechanistic impact of skeletal–vascular remodeling in CKD

Chronic kidney disease progressively impairs renal excretion of phosphate and a broad spectrum of protein-bound and middle-molecule uremic solutes (12). Among these, the gut microbiota–derived toxins indoxyl sulfate and p-cresyl sulfate are particularly relevant to CKD-MBD, since they accumulate early, bind avidly to plasma proteins, are poorly dialyzable, and exert pleiotropic

effects on immune, vascular, and bone cells (13). Indoxyl sulfate and p-cresyl sulfate originate from bacterial fermentation of dietary tryptophan and tyrosine/phenylalanine, followed by hepatic sulfation and reduced renal clearance in CKD. They engage oxidative stress pathways, activate transcription factors such as NF-κB and aryl hydrocarbon receptor, along with triggering of persistent low-grade inflammation. This condition, in turn reshapes mineral homeostasis and skeletal–vascular remodeling (14). In parallel, disruption of canonical mineral-regulating hormones, like parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), Klotho, and vitamin D constitutes a second major axis of immune–metabolic crosstalk. Previous authors found that, in early CKD, phosphate retention stimulates FGF23 secretion from osteocytes and osteoblasts, while declining renal function reduces Klotho expression, producing a state of FGF23 excess and Klotho deficiency that precedes overt hyperphosphatemia (15). Elevated FGF23 promotes phosphaturia and suppresses calcitriol synthesis, thereby contributing to secondary hyperparathyroidism and altered bone turnover, whereas Klotho deficiency is linked with vascular calcification, endothelial dysfunction, and accelerated vascular ageing (16). This hormonal milieu interacts with inflammatory cytokines and uremic toxins, forming a self-perpetuating network where immune activation aggravates mineral imbalance and vice versa (17). Several investigations is now detected, chronic inflammation as a central hallmark of CKD-MBD, driven jointly by uremic toxins, oxidative stress, gut dysbiosis, and metabolic acidosis (18). Monocytes, macrophages, T cells, and B cells exhibit a proinflammatory phenotype, secreting elevated levels of interleukin-6 (IL-6), tumor necrosis factor-α, IL-1β, and other mediators that act both systemically and locally in bone and vascular microenvironments (19). Pattern recognition receptors such as toll-like receptors and the NLRP3 inflammasome are activated by endogenous danger signals, bacterial products, and uremic toxins, further amplifying NF-κB and inflammasome signaling (20). In bone, this milieu enhances osteoclastogenesis through up-regulation of receptor activator of nuclear factor κB ligand (RANKL) and down-regulation of osteoprotegerin, whereas in vessels it drives vascular smooth muscle cell (VSMC) osteogenic transdifferentiation and calcification (21). The crosstalk between immune and metabolic pathways in CKD-MBD becomes particularly evident when examining the bone–vascular axis. Pathological vascular calcification is no longer considered a passive precipitation of calcium–phosphate but an active, cell-mediated process that shares key molecular signatures with bone formation, including induction of Runx2, bone morphogenetic protein 2 (BMP2), alkaline phosphatase, and osteocalcin in VSMCs (22). High phosphate and uremic toxins synergize to push VSMCs toward an osteoblast-like phenotype by MAPK, NF-κB, and Wnt/β-catenin pathways, while inflammatory cytokines and FGF23/Klotho imbalance modulate the intensity and pattern of this transformation (22). At the same time, bone remodeling is perturbed across the spectrum from high-turnover secondary hyperparathyroid bone disease, to low-turnover adynamic bone, with both extremes contributing to altered calcium–phosphate handling and worsening vascular calcification (23). In fact, indoxyl sulfate and p-cresyl sulfate exemplify how a single class of uremic solutes can simultaneously impinge on metabolism, immunity, bone, and vessels (13). Experimental models in rats with CKD have shown that continuous exposure to indoxyl sulfate or p-cresyl sulfate at concentrations comparable to those seen in patients significantly increases calcification in the aorta and peripheral arteries, independent of further deterioration in kidney function. These toxins upregulate acute-phase response and coagulation pathways and are associated with disturbances in glucose metabolism and insulin resistance, illustrating the link between metabolic dysfunction, inflammation, and vascular damage (24). In vitro, indoxyl sulfate induces endothelial dysfunction, promotes VSMC proliferation, and upregulates bone-related proteins, while p-cresyl sulfate interferes with osteoblast function and enhances oxidative stress, demonstrating direct toxicity on both vascular and bone cells (25). Clinically, higher circulating levels of these toxins correlate with increased vascular calcification, cardiovascular events, and mortality in CKD, reinforcing their role as key mediators of immune–metabolic injury (26). Beyond protein-bound toxins, alterations in gut microbiota composition contribute additional proinflammatory and procalcific stimuli (27). Gut dysbiosis in CKD favors urease- and protease-producing bacteria, increasing the generation of indoxyl sulfate, p-cresyl sulfate, and other gut-derived uremic toxins, while impaired intestinal barrier function allows translocation of endotoxin and microbial products into the circulation (28). These molecules engage TLR4 and other pattern recognition receptors on immune cells, endothelium, and bone cells, sustaining systemic inflammation and further modulating mineral and bone metabolism (29). The gut–kidney–bone–vascular axis thus emerges as an integrated system in which microbial metabolites, immune responses, and mineral hormones converge to shape CKD-MBD progression (30). Accordingly, the FGF23–Klotho axis exemplifies the endocrine arm of immune–metabolic crosstalk. In CKD, osteocytes markedly increase FGF23 production in response to phosphate retention, inflammation, and possibly to circulating uremic toxins (31). Elevated FGF23 enhances urinary phosphate excretion and inhibits renal 1α-hydroxylase, thereby lowering calcitriol levels and promoting secondary hyperparathyroidism. At the same time, Klotho expression in the kidney and vasculature

declines, impairing FGF23 signaling specificity and leading to off-target effects in tissues that lack Klotho (17). Whilst the impact of FGF23 on vascular calcification remains debated, with experimental data suggesting both protective and deleterious roles depending on context and Klotho expression, Klotho deficiency itself is consistently associated with increased vascular calcification and vascular stiffness (32). Moreover, FGF23 can induce left ventricular hypertrophy independent of Klotho, providing an additional cardiovascular pathway linked to CKD-MBD. Immune system activation intersects with the FGF23–Klotho axis at multiple levels (33). Proinflammatory cytokines like IL-6 and tumor necrosis factor-α enhance FGF23 transcription in bone cells, while FGF23 can modulate immune cell function and contribute to inflammation, creating a feed-forward loop (34). Klotho, conversely, exerts anti-inflammatory and antioxidative effects, and its deficiency amplifies NF-κB activation and oxidative stress in vascular and renal tissues. This reciprocal regulation illustrates how metabolic hormones and immune mediators form interconnected networks rather than acting in isolation (35). Within bone, the immune–metabolic interplay drives characteristic patterns of remodeling. Recent studies found that, CKD-MBD is associated with increased RANKL and decreased osteoprotegerin in bone and circulation, promoting osteoclast differentiation and bone resorption (36). Moreover, PTH, which is often elevated in CKD, further stimulates RANKL production by osteoblasts and osteocytes, exacerbating high-turnover bone disease. Inflammatory cytokines in the bone microenvironment enhance RANKL/RANK signaling and suppress osteoblast maturation, linking systemic inflammation to local skeletal pathology (37). Uremic toxins such as p-cresyl sulfate directly impair osteoblast function, reducing mineralization and promoting oxidative damage, which likely contributes to low bone formation rates seen in some CKD patients (38). The vascular compartment mirrors many aspects of skeletal mineralization, but in a maladaptive context. In CKD-MBD, VSMCs exposed to high phosphate, indoxyl sulfate, p-cresyl sulfate and inflammatory mediators undergo phenotypic switching toward osteoblast-like cells, with increased expression of Runx2, BMP2, alkaline phosphatase, and other osteogenic markers (39). In the meantime, phosphate excess activates MAPK and NF-κB signaling in VSMCs, while uremic toxins stimulate NLRP3 inflammasome and NF-κB pathways, enhancing osteogenic gene programs and matrix mineralization (40). Experimental work has shown that inhibition of NF-κB signaling, for example through zinc-induced up-regulation of the NF-κB inhibitor TNFAIP3, attenuates phosphate-induced vascular calcification, highlighting the centrality of immune pathways in this process (41). Furthermore, immune cells themselves infiltrate the vascular wall and calcified plaques in CKD, producing cytokines, matrix metalloproteinases, and osteogenic factors that further fuel calcification (42). Macrophages can release extracellular vesicles rich in calcium and phosphate, which act as nucleation sites for calcification and modulate VSMC phenotype (43). More recent studies detected that, B and T cells contribute to this microenvironment through cytokine production and, in the case of B cells, through altered osteoprotegerin production. Thus, vascular calcification in CKD-MBD emerges as an immunologically active remodeling process, more analogous to ectopic bone formation than to passive mineral deposition (36). The metabolic dimension of this crosstalk extends beyond traditional mineral parameters. Insulin resistance and dysregulated glucose metabolism are common in CKD and are linked to both uremic toxins and inflammatory signaling (44). Long-term p-cresyl sulfate exposure in CKD mice promotes insulin resistance and hyperglycemia, while indoxyl sulfate and p-cresyl sulfate in CKD rats associate with glucometabolic pathway activation and arterial calcification. These observations position uremic toxins at the intersection of metabolic syndrome–like features and vascular pathology (24). Inflammation itself contributes to insulin resistance, creating another bidirectional loop in which metabolic and immune dysregulation reinforce each other (45). Taken together, these intertwined pathways generate a "perfect storm" in which uremic toxins, chronic inflammation, disrupted mineral hormones, and metabolic dysfunction converge on bone and vascular tissues (46-48). In the skeleton, they drive an imbalance between osteoblast and osteoclast activity, resulting in altered bone turnover, impaired microarchitecture, fractures, and abnormal calcium and phosphate release or uptake (13). In the vasculature, they foster VSMC osteogenic transformation, matrix vesicle release, extracellular matrix remodeling, and progressive vascular calcification that stiffens arteries, raises pulse pressure, and predisposes to left ventricular hypertrophy and ischemic events (49). Importantly, bone and vessels communicate indirectly through shared regulators: bone-derived FGF23 and RANKL influence cardiovascular and immune function, while vascular calcification and stiffness feedback on renal hemodynamics and systemic blood pressure, accelerating CKD progression and further toxin accumulation (36). Hence, CKD-MBD as an immune–metabolic network rather than as isolated abnormalities in phosphate, calcium, or PTH has direct implications for therapy. Conventional approaches like phosphate binders, vitamin D analogues, calcimimetics, and dialytic strategies largely target mineral derangements, nevertheless their impact on systemic inflammation, gut-derived toxins, and Klotho deficiency is limited (36,50). Accordingly, developing strategies aim to modulate upstream drivers; since, interventions that restore gut microbial balance or reduce indoxyl sulfate or p-cresyl sulfate generation and absorption such as prebiotics, probiotics and adsorbents or low-protein diets with

adequate essential amino acids seek to attenuate uremic toxicity and inflammation at the source (51). In addition, pharmacologic manipulation of the FGF23–Klotho axis, including recombinant Klotho or antibodies targeting excessive FGF23, is under investigation to rebalance mineral metabolism while limiting off-target cardiovascular effects (28). At the vascular level, investigations are exploring agents that enhance endogenous calcification inhibitors like matrix Gla protein and fetuin-A, antioxidants that mitigate oxidative stress–driven calcification, and specific inhibitors of osteogenic signaling pathways in VSMCs (52). Likewise, in bone, tailored management of PTH levels and vitamin D status, avoidance of over-suppression of bone turnover, and consideration of anti-resorptive or anabolic agents in selected CKD patients may help preserve skeletal integrity and influence systemic mineral handling (53). More broadly, anti-inflammatory interventions, including stricter control of traditional cardiovascular risk factors, may confer dual benefits on both bone and vasculature by dampening the inflammatory component of CKD-MBD (36).

Conclusion

In conclusion, the pathophysiology of CKD-MBD extends far beyond traditional disturbances in calcium and phosphate homeostasis. Emerging evidence underscores a complex immune-metabolic crosstalk driven by the accumulation of uremic toxins and chronic systemic inflammation. This review highlights how protein-bound uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, act as pivotal mediators that exacerbate inflammatory signaling, disrupting the bone-vascular axis. The dysregulation observed is not merely passive but an active process where immune cell metabolism influences vascular calcification and bone demineralization simultaneously. Macrophage polarization and T-cell activation, fueled by metabolic reprogramming, contribute to an osteogenic switch in VSMCs while suppressing osteoblast function. Consequently, the clinical phenotype of concurrent vascular stiffening and skeletal fragility emerges as a direct consequence of this inflammatory-metabolic nexus. This confirms that vascular calcification and renal osteodystrophy are intertwined manifestations of the same underlying immune-metabolic disturbance. Therapeutically, these insights necessitate a paradigm shift. Managing CKD-MBD requires strategies that target the upstream drivers of immune-metabolic dysfunction, rather than solely correcting mineral levels. Potential interventions include enhanced toxin removal, specific anti-inflammatory agents, and metabolic modulators. Future research must prioritize delineating specific molecular pathways within this crosstalk to identify precise therapeutic targets. Ultimately, recognizing CKD-MBD as a systemic inflammatory-metabolic syndrome offers a promising avenue for reducing the excessive cardiovascular morbidity and mortality that define this condition. By integrating immunometabolism into clinical frameworks, we pave the way for more holistic, mechanism-based interventions that improve long-term survival and patient quality of life.

Authors' contribution

Conceptualization: Fariza Mukhammedova and Malika Saidova.
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Data curation: Malika Saidova, Faxriddin Madolimov, and Fariza Mukhammedova.
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Visualization: Elena Akhmedova and Mukhammad Amonov.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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References

1. Cai ZY, Hu XF, Chen LQ, Li ZR, Du XG. [A Cross-sectional Study of Osteoporosis and Cardiovascular Calcification in Patients with Chronic Kidney Disease at Different CKD Stages]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2021;52:334-9. doi: 10.12182/20210360507.
2. Reiss AB, Miyawaki N, Moon J, Kasselman LJ, Voloshyna I, D'Avino R, Jr., et al. CKD, arterial calcification, atherosclerosis and bone health: Inter-relationships and controversies. Atherosclerosis. 2018;278:49-59. doi: 10.1016/j.atherosclerosis.2018.08.046.
3. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal. 2014;20:1126-67. doi: 10.1089/ars.2012.5149.
4. Wojtaszek E, Oldakowska-Jedynak U, Kwiatkowska M, Glogowski T, Malyszko J. Uremic toxins, oxidative stress, atherosclerosis in chronic kidney disease, and kidney Transplantation. Oxid Med Cell Longev. 2021;2021:6651367. doi: 10.1155/2021/6651367.
5. André C, Bodeau S, Kamel S, Bennis Y, Caillard P. The AKI-to-CKD Transition: The Role of Uremic Toxins. Int J Mol Sci. 2023;24:16152. doi: 10.3390/ijms242216152.
6. Arefin S, Mudrovcic N, Hobson S, Pietrocola F, Ebert T, Ward LJ, et al. Early vascular aging in chronic kidney disease: focus on microvascular maintenance, senescence signature and potential therapeutics. Transl Res. 2025;275:32-47. doi: 10.1016/j.trsl.2024.11.001.
7. Vanholder R, Van Laecke S, Glorieux G. What is new in uremic toxicity? Pediatr Nephrol. 2008;23:1211-21. doi: 10.1007/s00467-008-0762-9.

8. Rosner MH, Reis T, Husain-Syed F, Vanholder R, Hutchison C, Stenvinkel P, et al. Classification of Uremic Toxins and Their Role in Kidney Failure. Clin J Am Soc Nephrol. 2021;16:1918-28. doi: 10.2215/cjn.02660221.
9. Lim YJ, Sidor NA, Tonial NC, Che A, Urquhart BL. Uremic toxins in the progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. Toxins (Basel). 2021;13:142. doi: 10.3390/toxins13020142.
10. Shah A, Hashmi MF, Aeddula NR. Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD). Treasure Island (FL): StatPearls Publishing LLC.; 2025.
11. Terai K, Nara H, Takakura K, Mizukami K, Sanagi M, Fukushima S, et al. Vascular calcification and secondary hyperparathyroidism of severe chronic kidney disease and its relation to serum phosphate and calcium levels. Br J Pharmacol. 2009;156:1267-78. doi: 10.1111/j.1476-5381.2008.00108.x.
12. van den Brand JA, Mutsaers HA, van Zuilen AD, Blankestijn PJ, van den Broek PH, Russel FG, et al. Uremic Solutes in Chronic Kidney Disease and Their Role in Progression. PLoS One. 2016;11:e0168117. doi: 10.1371/journal.pone.0168117.
13. Hung KC, Yao WC, Liu YL, Yang HJ, Liao MT, Chong K, et al. The potential influence of uremic toxins on the homeostasis of bones and muscles in chronic kidney disease. Biomedicines. 2023;11:2076. doi: 10.3390/biomedicines11072076.
14. Lu CL, Zheng CM, Lu KC, Liao MT, Wu KL, Ma MC. Indoxyl-sulfate-induced redox imbalance in chronic kidney disease. Antioxidants (Basel). 2021;10:936. doi: 10.3390/antiox10060936.
15. Bergwitz C, Jüppner H. Regulation of phosphate homeostasis by PTH, vitamin D, and FGF23. Annu Rev Med. 2010;61:91-104. doi: 10.1146/annurev.med.051308.111339.
16. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. Annu Rev Physiol. 2013;75:503-33. doi: 10.1146/annurev-physiol-030212-183727.
17. Vogt I, Haffner D, Leifheit-Nestler M. FGF23 and Phosphate-Cardiovascular Toxins in CKD. Toxins (Basel). 2019;11:647. doi: 10.3390/toxins11110647.
18. Evenepoel P, Stenvinkel P, Shanahan C, Pacifici R. Inflammation and gut dysbiosis as drivers of CKD-MBD. Nat Rev Nephrol. 2023;19:646-57. doi: 10.1038/s41581-023-00736-7.
19. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol. 2014;5:491. doi: 10.3389/fimmu.2014.00491.
20. Leemans JC, Kors L, Anders HJ, Florquin S. Pattern recognition receptors and the inflammasome in kidney disease. Nat Rev Nephrol. 2014;10:398-414. doi: 10.1038/nrneph.2014.91.
21. Song JH, Liu MY, Ma YX, Wan QQ, Li J, Diao XO, et al. Inflammation-associated ectopic mineralization. Fundam Res. 2023;3:1025-38. doi: 10.1016/j.fmre.2022.04.020.
22. Mace ML, Egstrand S, Morevati M, Olgaard K, Lewin E. New insights to the crosstalk between vascular and bone tissue in chronic kidney disease-mineral and bone disorder. Metabolites. 2021;11:849. doi: 10.3390/metabo11120849.
23. Roumpou A, Palermo A, Tournis S, Hasenmajer V, Pasieka JL, Kaltsas G, et al. Bone in parathyroid diseases revisited: evidence from epidemiological, surgical and new drug outcomes. Endocr Rev. 2025;46:576-620. doi: 10.1210/endrev/bnaf010.
24. Opdebeeck B, Maudsley S, Azmi A, De Maré A, De Leger W, Meijers B, et al. Indoxyl Sulfate and p-Cresyl Sulfate Promote Vascular Calcification and Associate with Glucose Intolerance. J Am Soc Nephrol. 2019;30:751-66. doi: 10.1681/asn.2018060609.
25. Kamprom W, Tawonsawatruk T, Mas-Oodi S, Anansilp K, Rattanasompattikul M, Supokawej A. P-cresol and indoxyl sulfate impair osteogenic differentiation by triggering mesenchymal stem cell senescence. Int J Med Sci. 2021;18:744-55. doi: 10.7150/ijms.48492.
26. Chermiti R, Burtey S, Dou L. Role of Uremic Toxins in Vascular Inflammation Associated with Chronic Kidney Disease. J Clin Med. 2024;13. doi: 10.3390/jcm13237149.
27. Graboski AL, Redinbo MR. Gut-Derived Protein-Bound Uremic Toxins. Toxins (Basel). 2020;12:590. doi: 10.3390/toxins12090590.
28. Rysz J, Franczyk B, Ławiński J, Olszewski R, Ciałkowska-Rysz A, Gluba-Brzózka A. The Impact of CKD on Uremic Toxins and Gut Microbiota. Toxins (Basel). 2021;13:252. doi: 10.3390/toxins13040252.
29. You Y, Xiang T, Yang C, Xiao S, Tang Y, Luo G, et al. Interactions between the gut microbiota and immune cell dynamics: novel insights into the gut-bone axis. Gut Microbes. 2025;17:2545417. doi: 10.1080/19490976.2025.2545417.
30. Alobaidi S. The gut-kidney axis in chronic kidney disease: mechanisms, microbial metabolites, and microbiome-targeted therapeutics. Front Med (Lausanne). 2025;12:1675458. doi: 10.3389/fmed.2025.1675458.
31. Komaba H, Fukagawa M. FGF23: a key player in mineral and bone disorder in CKD. Nefrologia. 2009;29:392-6. doi: 10.3265/Nefrologia.2009.29.5.5400.en.full.
32. Lindberg K, Olauson H, Amin R, Ponnusamy A, Goetz R, Taylor RF, et al. Arterial klotho expression and FGF23 effects on vascular calcification and function. PLoS One. 2013;8:e60658. doi: 10.1371/journal.pone.0060658.
33. Stöhr R, Schuh A, Heine GH, Brandenburg V. FGF23 in Cardiovascular Disease: Innocent Bystander or Active Mediator? Front Endocrinol (Lausanne). 2018;9:351. doi: 10.3389/fendo.2018.00351.
34. Fitzpatrick EA, Han X, Xiao Z, Quarles LD. Role of Fibroblast Growth Factor-23 in Innate Immune Responses. Front Endocrinol (Lausanne). 2018;9:320. doi: 10.3389/fendo.2018.00320.
35. Liang Y, Zhang Q, Qian JR, Li SS, Liu QF. Inflammation-Induced Klotho Deficiency: A Possible Key Driver of Chronic Kidney Disease Progression. Int J Gen Med. 2025;18:2507-20. doi: 10.2147/ijgm.S513497.
36. Xu B, Ma R, Wu Y, Liu C, Song X. Immune mechanisms in chronic kidney disease-mineral and bone disorder: current insights and therapeutic implications. Front Med (Lausanne). 2025;12:1678640. doi: 10.3389/fmed.2025.1678640.
37. Aguilar A, Gifre L, Ureña-Torres P, Carrillo-López N, Rodriguez-García M, Massó E, et al. Pathophysiology of bone disease in chronic kidney disease: from basics to renal osteodystrophy and osteoporosis. Front Physiol. 2023;14:1177829. doi: 10.3389/fphys.2023.1177829.
38. Yiang GT, Su WL, Zheng CM, Liao MT, Cheng TH, Lu CL, et al. The influence of uremic toxins on low bone turnover disease in chronic kidney disease. Tzu Chi Med J. 2024;36:38-45. doi: 10.4103/tcmj.tcmj_212_23.
39. Hruska KA, Mathew S, Lund RJ, Memon I, Saab G. The pathogenesis of vascular calcification in the chronic kidney disease mineral bone disorder: the links between bone and the vasculature. Semin Nephrol. 2009;29:156-65. doi: 10.1016/j.semnephrol.2009.01.008.
40. Lu Y, Meng L, Wang X, Zhang Y, Zhang C, Zhang M. The Non-Traditional Cardiovascular Culprits in Chronic Kidney Disease: Mineral Imbalance and Uremic Toxin Accumulation. Int J Mol Sci. 2025;26:7938. doi: 10.3390/ijms26167938.
41. Voelkl J, Tuffaha R, Luong TTD, Zickler D, Masyout J, Feger M, et al. Zinc Inhibits Phosphate-Induced Vascular Calcification

through TNFAIP3-Mediated Suppression of NF-κB. J Am Soc Nephrol. 2018;29:1636-48. doi: 10.1681/asn.2017050492.
42. Benz K, Varga I, Neureiter D, Campean V, Daniel C, Heim C, et al. Vascular inflammation and media calcification are already present in early stages of chronic kidney disease. Cardiovasc Pathol. 2017;27:57-67. doi: 10.1016/j.carpath.2017.01.004.
43. Li D, Fan C, Li X, Zhao L. The role of macrophage polarization in vascular calcification. Biochem Biophys Res Commun. 2024;710:149863. doi: 10.1016/j.bbrc.2024.149863.
44. Pieniazek A, Bernasinska-Slomczewska J, Gwozdzinski L. Uremic Toxins and Their Relation with Oxidative Stress Induced in Patients with CKD. Int J Mol Sci. 2021;22:6196. doi: 10.3390/ijms22126196.
45. Berbudi A, Khairani S, Tjahjadi AI. Interplay Between Insulin Resistance and Immune Dysregulation in Type 2 Diabetes Mellitus: Implications for Therapeutic Interventions. Immunotargets Ther. 2025;14:359-82. doi: 10.2147/itt.S499605.
46. Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. Nat Rev Endocrinol. 2012;8:529-43. doi: 10.1038/nrendo.2012.36.
47. Williams ME. Chronic kidney disease/bone and mineral metabolism: the imperfect storm. Semin Nephrol. 2009;29:97-104. doi: 10.1016/j.semnephrol.2009.01.002.
48. Towler DA. Chronic kidney disease: the "perfect storm" of cardiometabolic risk illuminates genetic diathesis in cardiovascular disease. J Am Coll Cardiol. 2013;62:799-801. doi: 10.1016/j.jacc.2013.04.063.
49. Jaminon A, Reesink K, Kroon A, Schurgers L. The Role of Vascular Smooth Muscle Cells in Arterial Remodeling: Focus on Calcification-Related Processes. Int J Mol Sci. 2019;20:5694. doi: 10.3390/ijms20225694.
50. Thompson E, Tashman A, Scialla JJ. Chronic Kidney Disease-Mineral and Bone Disorder Management in 4D: The Case for Dynamic Treatment Regime Methods to Optimize Care. Curr Osteoporos Rep. 2025;23:16. doi: 10.1007/s11914-025-00911-8.
51. Cedillo-Flores R, Cuevas-Budhart MA, Cavero-Redondo I, Kappes M, Ávila-Díaz M, Paniagua R. Impact of gut microbiome modulation on uremic toxin reduction in chronic kidney disease: a systematic review and network meta-analysis. Nutrients. 2025;17:1247. doi: 10.3390/nu17071247.
52. Yang S, Zeng Z, Yuan Q, Chen Q, Wang Z, Xie H, et al. Vascular calcification: from the perspective of crosstalk. Mol Biomed. 2023;4:35. doi: 10.1186/s43556-023-00146-y.
53. Hansen D, Jørgensen HS, Andersen TL, Ferreira AC, Ferreira A, de Jongh R, et al. Multidisciplinary team approach for CKD-associated osteoporosis. Nephrol Dial Transplant. 2024;40:48-59. doi: 10.1093/ndt/gfae197.