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# When kidneys and joints collide; bidirectional pathogenic crosstalk in CKD and osteoarthritis; from molecular mechanisms to clinical management

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**ABSTRACT**

Chronic kidney disease (CKD) and osteoarthritis frequently coexist, particularly in aging populations, imposing a significant burden on patients and healthcare systems. Emerging evidence reveals a complex, bidirectional pathogenic crosstalk between these conditions, extending beyond shared risk factors like aging and obesity. In CKD, the accumulation of uremic toxins, systemic inflammation driven by cytokines and disturbances in mineral bone disorder (CKD-MBD), characterized by dysregulated fibroblast growth factor-23 (FGF23), Klotho deficiency, hyperparathyroidism, and vascular calcification, actively contribute to accelerated articular cartilage degradation, synovitis, and subchondral bone sclerosis, thereby promoting osteoarthritis initiation and progression. Conversely, osteoarthritis-induced chronic pain, joint dysfunction, and reduced mobility lead to physical inactivity, sarcopenia, and metabolic dysregulation, potentially exacerbating CKD progression through strengthened inflammation, insulin resistance, and cardiovascular strain. This bidirectional relationship creates significant clinical challenges; since, standard osteoarthritis analgesics like non-steroidal anti-inflammatory drugs are nephrotoxic and contraindicated in chronic renal failure, since CKD-related complications complicate joint replacement surgery and rehabilitation. Effective management requires a paradigm shift towards integrated care. Treatment modalities include aggressive CKD-MBD control, cautious selection of joint-friendly analgesics, structured exercise programs tailored to renal and joint limitations, and early specialist collaboration. Identification of these intertwined molecular pathways is necessary for developing targeted therapies that simultaneously protect both renal and musculoskeletal health, eventually improving outcomes for this high-risk comorbid population.

*Implication for health policy/practice/research/medical education:*
Osteoarthritis, once simplistically labeled wear and tear, is now recognized as a whole-joint disease involving active pathological processes within the articular cartilage, subchondral bone, synovium, ligaments, and periarticular muscles. Low-grade inflammation driven by innate immune activation within the joint, dysregulated extracellular matrix metabolism, chondrocyte senescence, and aberrant subchondral bone remodeling are principal parameters for its initiation and progression. The conjunction of these two pathological landscapes, the systemic impacts of chronic kidney disease and inflammation state of chronic renal failure and also the localized joint-destructive processes of osteoarthritis, creates a suitable background for mutual exacerbation.

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Review

## Introduction

Chronic kidney disease (CKD) and osteoarthritis are two prevalent, debilitating conditions markedly affecting global health due to their high prevalence and complex interplay, especially in aging populations (1). Historically, both have been viewed as distinct entities, with CKD representing the progressive decline in renal function and metabolic functions, while osteoarthritis is predominantly regarded as a degenerative joint disease characterized by cartilage breakdown, synovial inflammation, and structural bone changes (2). However, accumulating experimental and clinical data have revealed that the relationship between kidney and joint disease is far more interconnected, characterized by a bidirectional exchange of pathogenic signals, shared molecular pathways, and overlapping risk factors that influence disease progression and clinical outcomes in both organ systems (2-4). Fundamentally, CKD and osteoarthritis not only share non-modifiable and environmental risk factors such as aging, obesity, chronic low-grade inflammation, and metabolic syndrome (1), but also their interaction is amplified through molecular mediators and systemic syndromes (2). The chronic kidney disease-mineral bone disorder (CKD-MBD) exemplifies this interface, affecting the intricate balance between renal, bone, and vascular health, and contributing to mineral metabolism derangements, vascular calcification, and abnormal bone turnover (5). In CKD, the retention of uremic toxins, altered phosphate and calcium balance, and dysregulation of fibroblast growth factor-23 (FGF23), parathyroid hormone, and vitamin D metabolism lead to systemic manifestations that pervade the skeleton (6). These changes result in bone fragility, subchondral bone remodeling, and increased susceptibility to osteoarthritis -like joint degeneration (2). Simultaneously, the synovial and chondrocytic milieu is modulated by circulating inflammatory cytokines and altered mineral homeostasis, further fostering joint deterioration (7). From an osteoarthritis perspective, joint disease incites a persistent inflammatory cascade in the affected tissue, producing an abundance of danger-associated molecular patterns, proinflammatory mediators, and matrix-degrading enzymes including matrix metalloproteinases (MMPs), notably MMP-13, which collectively contribute to cartilage loss, osteophyte formation or erosion, and synovial activation (8). In fact, osteoarthritis, which traditionally viewed as a localized joint disorder, is increasingly recognized for its systemic inflammatory impact. This inflammation, while originating locally, is not benign and extends beyond the joints to affect various organs and systems throughout the body (2,4). The systemic effects of osteoarthritis-driven inflammation are discernible and significant. They include renal endothelial dysfunction, which can impair kidney function. Furthermore, this inflammation propagates pro-apoptotic and fibrogenic signals, potentially leading to tissue damage and scarring in different organs (2-4). Moreover, osteoarthritis-related systemic inflammation can induce glomerular involvement, indicating a direct impact on glomeruli (2-4). These far-reaching consequences underscore the importance of considering osteoarthritis as a condition with both local and systemic implications, necessitating a broader perspective on its management and treatment. These bidirectional effects have been validated in mouse models where joint damage provokes renal fibrosis, and CKD alters joint microarchitecture by promoting bone resorption and modifying osteophyte development (9). This narrative review, therefore sought to consider bidirectional pathogenic crosstalk in CKD and osteoarthritis; from molecular mechanisms to clinical management.

## Search strategy

For this narrative review, a comprehensive literature search was conducted across multiple electronic databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy combined relevant controlled vocabulary and free-text terms—such as osteoarthritis, chronic kidney disease, fibroblast growth factor 23, chondrocytes, parathyroid hormone, and renal fibrosis—using appropriate Boolean operators to ensure broad yet focused retrieval of pertinent studies

## Mechanistic insight of chronic inflammation in CKD

In CKD, reduced renal clearance leads to accumulation of pro-inflammatory cytokines like interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-18 (IL-18), and tumor necrosis factor-alpha (TNF-α) (10). Uremic toxins, particularly indoxyl sulfate and p-cresyl sulfate, directly activate immune cells and endothelial cells, further fueling inflammation and oxidative stress (11). This systemic inflammatory milieu readily penetrates joint tissues. Within the synovium and cartilage, these circulating cytokines activate resident macrophages and fibroblasts, promoting synovitis (12). Critically, they also stimulate chondrocytes – the sole cells maintaining articular cartilage – to produce matrix-degrading enzymes like MMPs and aggrecanases, while simultaneously suppressing the synthesis of essential cartilage components like type II collagen and aggrecan (13). This imbalance accelerates cartilage breakdown (13). Furthermore, systemic inflammation sensitizes joint nociceptors, contributing significantly to the often-disabling pain experienced by patients with both conditions, pain that may be disproportionate to radiographic findings due to this neuroinflammatory component (14,15). Likewise, oxidative stress acts as a powerful amplifier in this vicious cycle. Previous investigation detected that, CKD is a state of profound oxidative stress due to reduced antioxidant capacity (e.g., glutathione depletion), increased

production of reactive oxygen species (ROS) from activated leukocytes and dysfunctional mitochondria, and accumulation of pro-oxidant uremic toxins (16). In the next step, ROS directly damage chondrocytes, inducing apoptosis and senescence (17). Senescent chondrocytes adopt a deleterious senescence-associated secretory phenotype (SASP), releasing a barrage of inflammatory cytokines, chemokines, and proteases that further degrade the cartilage matrix and propagate inflammation locally and systemically (18). Oxidative stress also impairs the function of vital cartilage-protective molecules and activates key signaling pathways like nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), which drive the expression of catabolic and inflammatory genes within joint tissues (19). The uremic environment itself is directly chondrotoxic (20). Toxins like indoxyl sulfate have been shown in-vitro to inhibit chondrocyte proliferation, induce apoptosis, suppress collagen type II synthesis, and upregulate MMP expression (21). Advanced glycation end products, which accumulate in CKD due to reduced clearance and increased formation in the context of hyperglycemia and oxidative stress, bind to their receptor on chondrocytes and synovial cells (2). This binding triggers intracellular signaling cascades that promote inflammation, oxidative stress, and the production of destructive enzymes, mimicking and exacerbating the core pathological processes of osteoarthritis (2). Then, advanced glycation end products accumulation directly stiffens the collagen network within cartilage, reducing its resilience to mechanical load (22). On the other hand, dysregulation of mineral and bone metabolism, as the hallmark of CKD-MBD, exerts profound effects on joint health (23). Hyperphosphatemia, a near-constant feature of progressive CKD, directly stimulates chondrocyte hypertrophy, which is associated with cartilage calcification and vulnerability to degradation (24,25). Elevated phosphate levels also promote vascular calcification, potentially compromising blood supply to subchondral bone and joint structures (26). FGF23, as a phosphaturic hormone that rises early and dramatically in CKD to counteract hyperphosphatemia, has emerged as a key pathogenic player beyond mineral balance (27). Chronically elevated FGF23, particularly in the context of Klotho deficiency can directly activate pro-inflammatory and pro-hypertrophic pathways in chondrocytes by FGFR4 signaling, independent of its phosphaturic effects (28). It should remember that, Klotho, as a co-receptor for FGF23, is predominantly produced in the kidney and declines steeply in CKD (29). This condition contributes to abnormal chondrocyte differentiation and matrix degradation (30). Secondary hyperparathyroidism, another pillar of CKD-MBD, involves markedly elevated parathyroid hormone levels (31). While intermittent parathormone exposure can be anabolic for bone, sustained high levels, as seen in CKD, promote bone resorption. This systemic bone loss can extend to the subchondral bone plate beneath articular cartilage (32). Furthermore, bone marrow lesions visible on MRI, associated with pain and progression in osteoarthritis, might be influenced by the altered bone turnover and microvascular disease prevalent in CKD (33). Vitamin D deficiency, nearly ubiquitous in CKD due to reduced renal 1-alpha-hydroxylation, impaired sunlight exposure, and dietary restrictions, also plays a detrimental role (34). Beyond its classical effects on calcium and bone, vitamin D possesses potent immunomodulatory properties. Deficiency promotes a pro-inflammatory state systemically and within the joint, reducing the synthesis of anti-inflammatory cytokines and failing to suppress destructive T-cell responses (35). Vitamin D also directly influences chondrocyte metabolism; its deficiency may impair cartilage matrix synthesis and promote catabolism (36).

## Impact of osteoarthritis on CKD progression

The bidirectional nature of this crosstalk of osteoarthritis and CKD becomes starkly evident when considering how this disease and its associated conditions can actively drive CKD progression (1). Obesity, a major risk factor for both knee osteoarthritis and CKD, is a primary instigator. Adipose tissue, particularly visceral fat, is not inert storage but a highly active endocrine organ secreting adipokines (37). Leptin, resistin, and visfatin are elevated in obesity and promote insulin resistance, systemic inflammation like increasing IL-6, TNF-α, CRP, and endothelial dysfunction (38). Leptin, in particular, has direct pro-fibrotic effects on renal tissue, stimulating mesangial cell proliferation and extracellular matrix production in the glomeruli, contributing to glomerulosclerosis (39). It also promotes podocyte injury and tubulointerstitial fibrosis (40). Adiponectin, often reduced in obesity, has protective anti-inflammatory and insulin-sensitizing effects; its relative deficiency further tips the balance towards inflammation and metabolic dysfunction (41). The mechanical stress of obesity on weight-bearing joints accelerates cartilage wear (42), but the metabolic consequences consisted of chronic inflammation, insulin resistance, dyslipidemia, directly damage the kidneys (43). Then, insulin resistance promotes glomerular hypertension and hyperfiltration, initiates inflammatory pathways within renal cells, and contributes to lipid accumulation in renal tubules (renal lipotoxicity), all accelerating CKD progression (44). In parallel, the systemic inflammation which originating from the osteoarthritis joint itself also feeds back into renal damage (1). While localized, the inflamed synovium releases cytokines and other mediators into the circulation (45). Chronic elevation of IL-1β, IL-6, and TNF-α can directly promote renal inflammation, fibrosis, and endothelial dysfunction (46). In addition, TNF-α can induce apoptosis in podocytes and tubular cells, disrupt

the glomerular filtration barrier, and stimulate the production of other fibrogenic factors like transforming growth factor-beta within the kidney. This condition creates a scenario where joint inflammation becomes a systemic driver of renal decline (47,48).

### Focus on cellular senescence

Cellular senescence and impaired regenerative capacity are central to the interaction. Kidneys in CKD show accumulation of senescent cells in tubular and interstitial compartments; these cells secrete SASP factors that sustain inflammation and fibrogenesis (49). Similarly, senescent chondrocytes and synovial fibroblasts in osteoarthritis produce SASP, which propagates matrix catabolism and attracts inflammatory cells (50). Systemic propagation of senescence signals, either by circulating SASP components, extracellular vesicles, or endocrine mediators could plausibly promote senescence in distant organs, linking kidney failure to accelerated joint aging (51). Experimental data indicated that uremic toxins can induce senescence-associated markers in peripheral tissues (52); whether this contributes to osteoarthritis acceleration in humans requires more study, since this concept provides a unifying mechanistic framework and a rationale for therapies that target senescence pathways, such as senolytics or SASP modulators, to mitigate multimorbidity risks (2,52).

### Treatment modalities

Management of this dual pathology is fraught with therapeutic dilemmas, primarily centered on pain control. Non-steroidal anti-inflammatory drugs (NSAIDs), a cornerstone of osteoarthritis pain management, are often contraindicated or require extreme caution in CKD (2). These agents inhibit renal prostaglandin synthesis, which is critical for maintaining renal blood flow, particularly in states of reduced effective circulating volume (53). This state can precipitate acute kidney injury, accelerates CKD progression, cause sodium and water retention exacerbating hypertension and edema, and increase the risk of hyperkalemia (53). Even short-term or low-dose of NSAID use carries significant risk, especially in stages 4-5 CKD (54). Acetaminophen is generally considered the first-line analgesic for mild-moderate osteoarthritis pain in CKD due to its favorable renal safety profile at recommended doses (55). However, concerns exist regarding potential hepatotoxicity with chronic high-dose administration and, more controversially, some epidemiological data suggesting a possible association with increased hypertension risk or accelerated CKD progression at very high cumulative doses, though causality remains unproven (56). Its efficacy for moderate-severe osteoarthritis pain is often limited (57). Topical analgesics offer a valuable renal-sparing alternative. Topical NSAIDs have minimal systemic absorption and are generally safe in CKD, providing effective localized pain relief for accessible joints like knees and hands (58). Topical capsaicin can be effective for neuropathic pain components but requires consistent application and causes initial burning sensation (59). Lidocaine patches are useful for localized neuropathic pain (60). Intra-articular therapies require careful consideration. Corticosteroid injections provide potent, albeit temporary, anti-inflammatory effects within the joint (61). While systemic absorption is low, repeated injections in CKD patients, especially those with diabetes, carry risks of local tissue atrophy, infection, and potentially transient hyperglycemia (61). Theoretical concerns exist about systemic effects on bone mineral density with frequent use, though evidence is limited (62). Hyaluronic acid viscosupplementation aims to restore the viscoelastic properties of synovial fluid. Its safety profile in CKD is generally considered favorable as it acts locally, but robust efficacy data specifically in CKD populations is lacking (63). Platelet-rich plasma and stem cell injections are emerging but remain experimental (64); however, their safety and efficacy in the uremic milieu are completely unknown and not currently recommended outside rigorous clinical trials. It is noteworthy to remember that non-pharmacological strategies become the cornerstone of management (2,64). Weight loss is paramount for overweight or obese patients, offering dual benefits: reducing mechanical stress on joints and mitigating the adipokine-driven inflammation that harms both joints and kidneys (65). However, achieving significant weight loss in advanced CKD is challenging due to dietary restrictions, reduced physical capacity, anorexia, and metabolic alterations (66). Tailored, renal-appropriate dietary counseling focusing on high-quality protein within prescribed limits, controlled potassium/phosphate intake, and calorie control is essential (67). Physical activity and exercise are non-negotiable but must be carefully prescribed. Low-impact aerobic exercise, strength training to support joints and combat sarcopenia, and flexibility exercises improve pain, function, cardiovascular health, and insulin sensitivity (68). Exercise programs must be individualized, starting slowly, accounting for fatigue, anemia, fluid status, and cardiovascular comorbidities common in CKD (69). Physical and occupational therapists experienced in both CKD and musculoskeletal conditions are invaluable assets (70). Moreover, assistive devices reduce joint loading and improve mobility and safety, crucial for preventing falls. Finally, patient education on joint protection techniques, energy conservation, and realistic goal setting is vital for self-management (71).

## Conclusion

In this review, we emphasized on the bidirectional link between CKD and osteoarthritis, emphasizing on a largely overlooked clinical paradigm. Recent studies found that,

these conditions are interconnected through shared pathophysiological mechanisms. In CKD, uremic toxins, mineral imbalance, chronic inflammation, and oxidative stress, create a feedback loop that accelerates joint degeneration by inducing chondrocyte death, synovitis, and subchondral bone changes. Conversely, osteoarthritis-related immobility and systemic inflammation can worsen renal fibrosis and functional decline. This interplay accentuates the need for a fundamental shift in clinical management. Conventional osteoarthritis treatments like NSAIDs may harm kidney function, while CKD management often neglects musculoskeletal health. Therefore, early detection through screening for osteoarthritis in CKD patients and vice versa is crucial. Personalized care strategies should focus on nephroprotective analgesics, tailored physical activity programs, and aggressive control of systemic inflammation and mineral disturbances. Future therapies should target shared pathogenic pathways, including reducing uremic toxins with prebiotics or adsorbents, applying anti-cytokine agents, and restoring Klotho levels. Hence collaboration among nephrologists, rheumatologists, and orthopedic specialists is necessary to deliver care. Recognizing the systemic, interconnected nature of CKD and osteoarthritis advocates for integrated therapeutic approaches that address both diseases simultaneously, ultimately improving outcomes and quality of life for vulnerable patients.

## Authors' contribution

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**Writing–original draft:** All authors.
**Writing–review and editing:** All authors.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

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

## 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.

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## References

1. Gao K, Zhang C, Zhang Y, Zhang L, Xu J, Xue H, et al. Is chronic kidney disease associated with osteoarthritis? The United States national health and nutrition examination survey 2011-2020. BMC Nephrol. 2024;25:236. doi: 10.1186/s12882-024-03672-1.
2. Yang RS, Chan DC, Chung YP, Liu SH. Chronic Kidney Disease and Osteoarthritis: Current Understanding and Future Research Directions. Int J Mol Sci. 2025;26:1567. doi: 10.3390/ijms26041567.
3. Pang L, Wu K, Zhu Y, Wang Q, Zheng Z, Lv C, et al. Osteoarthritis is a risk factor for renal function injury based on the National Health and Nutrition Examination Survey and Mendelian Randomized study. Sci Rep. 2025;15:12540. doi: 10.1038/s41598-025-97756-z.
4. Knights AJ, Redding SJ, Maerz T. Inflammation in osteoarthritis: the latest progress and ongoing challenges. Curr Opin Rheumatol. 2023;35:128–34. doi: 10.1097/bor.0000000000000923.
5. Hruska KA, Sugatani T, Agapova O, Fang Y. The chronic kidney disease - Mineral bone disorder (CKD-MBD): Advances in pathophysiology. Bone. 2017;100:80–6. doi: 10.1016/j.bone.2017.01.023.
6. Diniz H, Frazão JM. The role of fibroblast growth factor 23 in chronic kidney disease-mineral and bone disorder. Nefrologia. 2013;33:835–44. doi: 10.3265/Nefrologia.pre2013.Jul.12091.
7. Hu K, Song M, Song T, Jia X, Song Y. Osteoimmunology in Osteoarthritis: Unraveling the Interplay of Immunity, Inflammation, and Joint Degeneration. J Inflamm Res. 2025;18:4121–42. doi: 10.2147/jir.S514002.
8. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012;64:1697–707. doi: 10.1002/art.34453.
9. Tan B, Tang W, Zeng Y, Liu J, Du X, Su H, et al. Development of animal models with chronic kidney disease-mineral and bone disorder based on clinical characteristics and pathogenesis. Front Endocrinol (Lausanne). 2025;16:1549562. doi: 10.3389/fendo.2025.1549562.
10. Kadatane SP, Satariano M, Massey M, Mongan K, Raina R. The Role of Inflammation in CKD. Cells. 2023;12:1581. doi: 10.3390/cells12121581.
11. Harlacher E, Wollenhaupt J, Baaten C, Noels H. Impact of uremic toxins on endothelial dysfunction in chronic kidney disease: a systematic review. Int J Mol Sci. 2022;23:531. doi: 10.3390/ijms23010531.
12. Jiang T, Su S, Tian R, Jiao Y, Zheng S, Liu T, et al. Immunoregulatory orchestrations in osteoarthritis and mesenchymal stromal cells for therapy. J Orthop Translat. 2025;55:38–54. doi: 10.1016/j.jot.2025.08.009.
13. Mukherjee A, Das B. The role of inflammatory mediators and matrix metalloproteinases (MMPs) in the progression of osteoarthritis. Biomater Biosyst. 2024;13:100090. doi: 10.1016/j.bbiosy.2024.100090.
14. Alad M, Yousef F, Epure LM, Lui A, Grant MP, Merle G, et al. Unraveling osteoarthritis: mechanistic insights and emerging therapies targeting pain and inflammation. Biomolecules. 2025;15:874. doi: 10.3390/biom15060874.
15. Kelleher EM, Meouchi R, Irani A. Beyond Inflammation: Why Understanding the Brain Matters in Inflammatory Arthritis. Arthritis Care Res (Hoboken). 2026;78:3-14. doi: 10.1002/acr.25694.
16. Okamura DM, Pennathur S. The balance of powers: Redox regulation of fibrogenic pathways in kidney injury. Redox Biol. 2015;6:495–504. doi: 10.1016/j.redox.2015.09.039.
17. Bolduc JA, Collins JA, Loeser RF. Reactive oxygen species, aging and articular cartilage homeostasis. Free Radic Biol Med. 2019;132:73–82. doi: 10.1016/j.freeradbiomed.2018.08.038.
18. Coryell PR, Diekman BO, Loeser RF. Mechanisms

and therapeutic implications of cellular senescence in osteoarthritis. Nat Rev Rheumatol. 2021;17:47–57. doi: 10.1038/s41584-020-00533-7.
19. Ziskoven C, Jäger M, Zilkens C, Bloch W, Brixius K, Krauspe R. Oxidative stress in secondary osteoarthritis: from cartilage destruction to clinical presentation? Orthop Rev (Pavia). 2010;2:e23. doi: 10.4081/or.2010.e23.
20. Lanza D, Perna AF, Oliva A, Vanholder R, Pletinck A, Guastafierro S, et al. Impact of the uremic milieu on the osteogenic potential of mesenchymal stem cells. PLoS One. 2015;10:e0116468. doi: 10.1371/journal.pone.0116468.
21. Kim YH, Kwak KA, Gil HW, Song HY, Hong SY. Indoxyl sulfate promotes apoptosis in cultured osteoblast cells. BMC Pharmacol Toxicol. 2013;14:60. doi: 10.1186/2050-6511-14-60.
22. Verzijl N, DeGroot J, Ben ZC, Brau-Benjamin O, Maroudas A, Bank RA, et al. Crosslinking by advanced glycation end products increases the stiffness of the collagen network in human articular cartilage: a possible mechanism through which age is a risk factor for osteoarthritis. Arthritis Rheum. 2002;46:114–23. doi: 10.1002/1529-0131(200201)46:1<114::Aid-art10025>3.0.Co;2-p.
23. Shah A, Hashmi MF, Aeddula NR. Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD). Treasure Island (FL): StatPearls Publishing Publishing LLC.; 2025.
24. Stassen R, van den Akker GGH, Caron MMJ, Surtel DAM, Cremers A, van Rhijn LW, et al. TGF-β Enhances Phosphate-Driven Calcification of Human OA Articular Chondrocytes. Calcif Tissue Int. 2025;116:57. doi: 10.1007/s00223-025-01365-x.
25. Miedlich SU, Zalutskaya A, Zhu ED, Demay MB. Phosphate-induced apoptosis of hypertrophic chondrocytes is associated with a decrease in mitochondrial membrane potential and is dependent upon Erk1/2 phosphorylation. J Biol Chem. 2010;285:18270–5. doi: 10.1074/jbc.M109.098616.
26. Giachelli CM. The emerging role of phosphate in vascular calcification. Kidney Int. 2009;75:890–7. doi: 10.1038/ki.2008.644.
27. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. Kidney Int. 2012;82:737–47. doi: 10.1038/ki.2012.176.
28. Richter B, Faul C. FGF23 Actions on Target Tissues-With and Without Klotho. Front Endocrinol (Lausanne). 2018;9:189. doi: 10.3389/fendo.2018.00189.
29. Hu MC, Kuro-o M, Moe OW. The emerging role of Klotho in clinical nephrology. Nephrol Dial Transplant. 2012;27:2650–7. doi: 10.1093/ndt/gfs160.
30. Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res. 2011;109:697–711. doi: 10.1161/circresaha.110.234914.
31. Tsai SH, Kan WC, Jhen RN, Chang YM, Kao JL, Lai HY, et al. Secondary hyperparathyroidism in chronic kidney disease: A narrative review focus on therapeutic strategy. Clin Med (Lond). 2024;24:100238. doi: 10.1016/j.clinme.2024.100238.
32. Nguyen VL, Lee KB, Moon YJ. Parathyroid Hormone as a Modulator of Skeletal Muscle: Insights into Bone-Muscle and Nerve-Muscle Interactions. Int J Mol Sci. 2025;26:7060. doi: 10.3390/ijms26157060.
33. Pimentel A, Bover J, Elder G, Cohen-Solal M, Ureña-Torres PA. The use of imaging techniques in chronic kidney disease-mineral and bone disorders (CKD-MBD) - a systematic review. Diagnostics (Basel). 2021;11:772. doi: 10.3390/diagnostics11050772.
34. Chonchol M, Kendrick J, Targher G. Extra-skeletal effects of vitamin D deficiency in chronic kidney disease. Ann Med. 2011;43:273–82. doi: 10.3109/07853890.2010.543923.
35. Fenercioglu AK. The Anti-Inflammatory Roles of Vitamin D for Improving Human Health. Curr Issues Mol Biol. 2024;46:13514–25. doi: 10.3390/cimb46120807.
36. Garfinkel RJ, Dilisio MF, Agrawal DK. Vitamin D and Its Effects on Articular Cartilage and Osteoarthritis. Orthop J Sports Med. 2017;5:2325967117711376. doi: 10.1177/2325967117711376.
37. Shumnalieva R, Kotov G, Monov S. Obesity-related knee osteoarthritis-current concepts. Life (Basel). 2023;13:1650. doi: 10.3390/life13081650.
38. Al-Suhaimi EA, Shehzad A. Leptin, resistin and visfatin: the missing link between endocrine metabolic disorders and immunity. Eur J Med Res. 2013;18:12. doi: 10.1186/2047-783x-18-12.
39. Wolf G, Hamann A, Han DC, Helmchen U, Thaiss F, Ziyadeh FN, et al. Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: potential role in glomerulosclerosis [seecomments]. Kidney Int. 1999;56:860–72. doi: 10.1046/j.1523-1755.1999.00626.x.
40. McPherson KC, Taylor L, Johnson AC, Didion SP, Geurts AM, Garrett MR, et al. Early development of podocyte injury independently of hyperglycemia and elevations in arterial pressure in nondiabetic obese Dahl SS leptin receptor mutant rats. Am J Physiol Renal Physiol. 2016;311:F793–f804. doi: 10.1152/ajprenal.00590.2015.
41. Han Y, Sun Q, Chen W, Gao Y, Ye J, Chen Y, et al. New advances of adiponectin in regulating obesity and related metabolic syndromes. J Pharm Anal. 2024;14:100913. doi: 10.1016/j.jpha.2023.12.003.
42. Mocanu V, Timofte DV, Zară-Dănceanu CM, Labusca L. Obesity, metabolic syndrome, and osteoarthritis require integrative understanding and management. biomedicines. 2024;12:1262. doi: 10.3390/biomedicines12061262.
43. Jiang Z, Wang Y, Zhao X, Cui H, Han M, Ren X, et al. Obesity and chronic kidney disease. Am J Physiol Endocrinol Metab. 2023;324:E24–e41. doi: 10.1152/ajpendo.00179.2022.
44. Bansal A, Chonchol M. Metabolic dysfunction-associated kidney disease: pathogenesis and clinical manifestations. Kidney Int. 2025;108:194–200. doi: 10.1016/j.kint.2025.01.044.
45. de Lange-Brokaar BJ, Ioan-Facsinay A, van Osch GJ, Zuurmond AM, Schoones J, Toes RE, et al. Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. Osteoarthritis Cartilage. 2012;20:1484–99. doi: 10.1016/j.joca.2012.08.027.
46. Meng XM. Inflammatory Mediators and Renal Fibrosis. Adv Exp Med Biol. 2019;1165:381–406. doi: 10.1007/978-981-13-8871-2_18.
47. Wan Q, Zhou J, Wu Y, Shi L, Liu W, Ou J, et al. TNF-α-mediated podocyte injury via the apoptotic death receptor pathway in a mouse model of IgA nephropathy. Ren Fail. 2022;44:1216–26. doi:10.1080/0886022x.2022.2079527.
48. Lv W, Booz GW, Wang Y, Fan F, Roman RJ. Inflammation and renal fibrosis: Recent developments on key signaling molecules as potential therapeutic targets. Eur J Pharmacol. 2018;820:65–76. doi: 10.1016/j.ejphar.2017.12.016.
49. Zhao JL, Qiao XH, Mao JH, Liu F, Fu HD. The interaction between cellular senescence and chronic kidney disease as a therapeutic opportunity. Front Pharmacol. 2022;13:974361. doi: 10.3389/fphar.2022.974361.
50. Zhang XX, He SH, Liang X, Li W, Li TF, Li DF. Aging, Cell Senescence, the Pathogenesis and Targeted Therapies of Osteoarthritis. Front Pharmacol. 2021;12:728100. doi: 10.3389/fphar.2021.728100.
51. Khosla S, Farr JN, Tchkonia T, Kirkland JL. The role of cellular

senescence in ageing and endocrine disease. Nat Rev Endocrinol. 2020;16:263–75. doi: 10.1038/s41574-020-0335-y.
52. Yang Y, Mihajlovic M, Janssen MJ, Masereeuw R. The uremic toxin indoxyl sulfate accelerates senescence in kidney proximal tubule cells. Toxins (Basel). 2023;15:242. doi: 10.3390/toxins15040242.
53. Kim GH. Renal effects of prostaglandins and cyclooxygenase-2 inhibitors. Electrolyte Blood Press. 2008;6:35–41. doi: 10.5049/ebp.2008.6.1.35.
54. Baker M, Perazella MA. NSAIDs in CKD: Are They Safe? Am J Kidney Dis. 2020;76:546–57. doi: 10.1053/j.ajkd.2020.03.023.
55. Kanchanasurakit S, Arsu A, Siriplabpla W, Duangjai A, Saokaew S. Acetaminophen use and risk of renal impairment: A systematic review and meta-analysis. Kidney Res Clin Pract. 2020;39:81–92. doi: 10.23876/j.krcp.19.106.
56. Park WY. Controversies in acetaminophen nephrotoxicity. Kidney Res Clin Pract. 2020;39:4–6. doi: 10.23876/j.krcp.20.027.
57. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev. 2006;2006:Cd004257. doi: 10.1002/14651858.CD004257.pub2.
58. Shi C, Ye Z, Shao Z, Fan B, Huang C, Zhang Y, et al. Multidisciplinary Guidelines for the Rational Use of Topical Non-Steroidal Anti-Inflammatory Drugs for Musculoskeletal Pain (2022). J Clin Med. 2023;12:1544. doi: 10.3390/jcm12041544.
59. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth. 2011;107:490–502. doi: 10.1093/bja/aer260.
60. Hans G, Robert D, Verhulst J, Vercauteren M. Lidocaine 5% patch for localized neuropathic pain: progress for the patient, a new approach for the physician. Clin Pharmacol. 2010;2:65–70. doi: 10.2147/cpaa.S9795.
61. Singer B, Chaimovitz D, Bucek T, Dayon E, Abbott-Korumi A, Spatz M, et al. Corticosteroid Use in Musculoskeletal and Neuraxial Interventions: Effects on Glycemic Control. Medicina (Kaunas). 2025;61:936. doi: 10.3390/medicina61050936.
62. Walsh LJ, Lewis SA, Wong CA, Cooper S, Oborne J, Cawte SA, et al. The impact of oral corticosteroid use on bone mineral density and vertebral fracture. Am J Respir Crit Care Med. 2002;166:691–5. doi: 10.1164/rccm.2110047.
63. Marinho A, Nunes C, Reis S. Hyaluronic Acid: A Key Ingredient in the Therapy of Inflammation. Biomolecules. 2021;11. doi: 10.3390/biom11101518.
64. Schneider N, Sinnott M, Patel N, Joseph R. The Use of Platelet-Rich Plasma and Stem Cell Injections in Musculoskeletal Injuries. Cureus. 2024;16:e59970. doi: 10.7759/cureus.59970.
65. Hall JE, Mouton AJ, da Silva AA, Omoto ACM, Wang Z, Li X, et al. Obesity, kidney dysfunction, and inflammation: interactions in hypertension. Cardiovasc Res. 2021;117:1859–76. doi: 10.1093/cvr/cvaa336.
66. Capizzi I, Teta L, Vigotti FN, Tognarelli G, Consiglio V, Scognamiglio S, et al. Weight Loss in Advanced Chronic Kidney Disease: Should We Consider Individualised, Qualitative, ad Libitum Diets? A Narrative Review and Case Study. Nutrients. 2017;9:1109. doi: 10.3390/nu9101109.
67. Kim SM, Jung JY. Nutritional management in patients with chronic kidney disease. Korean J Intern Med. 2020;35:1279–90. doi: 10.3904/kjim.2020.408.
68. Moretti A, Tomaino F, Paoletta M, Liguori S, Migliaccio S, Rondanelli M, et al. Physical exercise for primary sarcopenia: an expert opinion. Front Rehabil Sci. 2025;6:1538336. doi: 10.3389/fresc.2025.1538336.
69. Kirkman DL, Bohmke N, Carbone S, Garten RS, Rodriguez-Miguelez P, Franco RL, et al. Exercise intolerance in kidney diseases: physiological contributors and therapeutic strategies. Am J Physiol Renal Physiol. 2021;320:F161–f73. doi: 10.1152/ajprenal.00437.2020.
70. Nussbaum J, Garcia RK. Restorative physical and occupational therapy: a critical need for patients with chronic kidney and end-stage renal disease. Adv Chronic Kidney Dis. 2009;16:529–35. doi: 10.1053/j.ackd.2009.08.001.
71. Bobos P, MacDermid JC, Nazari G, Lalone EA, Ferreira L, Grewal R. Joint Protection Programmes for People with Osteoarthritis and Rheumatoid Arthritis of the Hand: An Overview of Systematic Reviews. Physiother Can. 2021;73:56–65. doi: 10.3138/ptc-2019-0037.