https://nephropathol.com DOI: 10.34172/jnp.28722 J Nephropathol. 2026;15(4):e28722

Journal of Nephropathology

Mitochondrial dysfunction and renal tubular injury in malignancy-associated hypercalcemia; a mechanistic framework for acute kidney injury in advanced renal cancer

Zahed Karimi[1], Fariba Jafari Khabaz[2], Elham Kebriyaei[3], Ahmadreza Maghsoudi[4], Feruza Djalolova[5], Karimov Zafar[6], Dilbar Kurbanova[7], Tolliboyeva Marjona[8], Abdulloev Mukhriddin[9], Naeem Nikpour[10*]

[1]Department of Internal Medicine, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[2]Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[3]Clinical Research Development Unit, Valiasr Hospital, Fasa University of Medical Sciences, Fasa, Iran
[4]Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[5]Department of Oncology, Andijan State Medical Institute, Andijan, Uzbekistan
[6]Department of Radiation Diagnostics and Therapy, Samarkand State Medical University, Samarkand, Uzbekistan
[7]Department of Children's Diseases, Tashkent State Medical University, Tashkent, Uzbekistan
8Fergana Medical Institute of Public Health, Fergana, Uzbekistan
9Department of Infectious Diseases and Infectious Diseases of Children, Bukhara State Medical Institute named after Abu Ali ibn Sino, Bukhara, Uzbekistan
[10]Department of Hematology and Medical Oncology, Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran

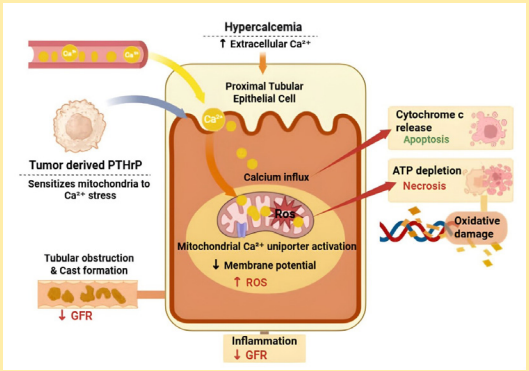
ARTICLE INFO

Article type:
Review

Article history:
Received: 11 Feb. 2026
Revised: 27 Apr. 2026
Accepted: 10 May 2026
Published online: 25 May 2026

Keywords:
Malignancy, Parathyroid hormone, Hypercalcemia, Parathyroid hormone–related peptide, Renal cell carcinoma, Acute kidney injury, Mitochondria, Oxidative stress, Glomerular filtration rate

ABSTRACT



Malignancy-associated hypercalcemia represents a severe metabolic complication frequently observed in advanced renal cell carcinoma (RCC), often precipitating acute kidney injury (AKT) and limiting therapeutic options. Though systemic volume depletion and renal vasoconstriction contribute to renal disturbance, direct tubular toxicity mediated by intrinsic mitochondrial dysfunction remains underexplored. This review discusses on mechanistic framework linking excessive extracellular calcium load to renal tubular epithelial failure. Hypercalcemia induces profound intracellular calcium overload within proximal tubular cells, triggering mitochondrial calcium uniporter activation. Consequently, mitochondrial membrane potential collapses due to permeability transition pore opening, effectively uncoupling oxidative phosphorylation. This bioenergetic crisis generates excessive reactive oxygen species (ROS), promoting lipid peroxidation, protein oxidation and DNA damage. Simultaneously, cytochrome c release initiates apoptotic cascades, whereas severe ATP depletion triggers necrotic cell death. The resulting tubular obstruction, cast formation, and inflammation exacerbate glomerular filtration rate loss. Furthermore, tumor-derived factors like parathyroid hormone-related protein (PTHrP) may sensitize mitochondria to calcium-induced stress, amplifying injury. Dysregulated mitochondrial dynamics, including fission and fusion imbalance, further compromise cellular resilience against calcium stress. Identification this pathway highlights mitochondria as critical therapeutic targets beyond standard hydration and bisphosphonates. Interventions stabilizing mitochondrial integrity, modulating calcium handling, or scavenging ROS could mitigate tubular injury. Eventually, deciphering these molecular events offers novel strategies to preserve renal function in patients with advanced renal cancer suffering from hypercalcemic crises. Such approaches may significantly improve survival outcomes and enable continued systemic therapy, addressing a critical unmet need in oncology nephrology where renal preservation dictates treatment eligibility and quality of life during palliative care.

*Corresponding author: Naeem Nikpour, Email: Dr.nikpour1360@gmail.com

Review

Implication for health policy/practice/research/medical education:
Malignancy-associated hypercalcemia frequently complicates advanced renal cancer, driving acute kidney injury (AKT) through distinct mechanistic pathways involving cellular energy failure. Elevated serum calcium induces renal vasoconstriction and direct tubular toxicity, mediated by severe mitochondrial dysfunction. Excessive intracellular calcium overload disrupts mitochondrial membrane potential, triggering oxidative stress and impairing ATP production essential for cellular homeostasis. This bioenergetic failure compromises proximal tubular integrity, leading to widespread cell death by apoptosis and necrosis. Consequently, glomerular filtration rate deteriorates sharply, exacerbating uremic toxicity. Calcium crystals within tubules exacerbate obstruction and inflammation, creating vicious injury cycles. This framework highlights mitochondria as critical hubs linking systemic hypercalcemia to tubular injury. Recognizing this pathway is vigorous for developing targeted therapies beyond standard hydration and bisphosphonates. Protecting mitochondrial function could mitigate AKT severity, improving overall outcomes in patients with advanced renal malignancies. Eventually, addressing calcium-mediated mitochondrial toxicity offers a promising strategy to preserve renal function during aggressive cancer progression..
Please cite this paper as: Karimi Z, Jafari Khabaz F, Kebriyaei E, Maghsoudi A, Djalolova F, Zafar K, Kurbanova D, Marjona T, Mukhriddin A, Nikpour N. Mitochondrial dysfunction and renal tubular injury in malignancy-associated hypercalcemia; a mechanistic framework for acute kidney injury in advanced renal cancer. J Nephropathol. 2026;15(4):e28722. DOI: 10.34172/jnp.28722.

Introduction

Malignancy-associated hypercalcemia is one of the most frequent and life-threatening metabolic complications of advanced solid tumors, including renal cell carcinoma (RCC), and it is tightly linked to the development of acute kidney injury (AKI) (1,2). A coherent mechanistic framework for AKI in advanced renal cancer needs to integrate systemic drivers of hypercalcemia, intrarenal hemodynamic and tubular transport changes, and cell-level mitochondrial injury within the renal tubule (1). Malignancy-associated hypercalcemia in RCC is predominantly a paraneoplastic phenomenon and often signals biologically aggressive disease with high tumor burden or metastasis (2). In RCC, hypercalcemia most commonly arises from overproduction of parathyroid hormone–related peptide (PTHrP) as the humoral hypercalcemia of malignancy, less frequently from ectopic calcitriol production, and occasionally from extensive osteolytic metastases that release calcium and pro-osteoclastogenic cytokines (3). In fact, PTHrP mimics the biological actions of parathyroid hormone (PTH) at the PTH/PTHrP receptor in bone and kidney, enhancing osteoclastic bone resorption and renal tubular calcium reabsorption, while endogenous PTH is typically suppressed (4). Other tumor-derived mediators such as interleukin-6, tumor necrosis factor-α, transforming growth factor-β, and prostaglandins can amplify bone resorption and alter vitamin D metabolism, creating a cytokine-driven milieu that sustains hypercalcemia (5). From the renal standpoint, the acute consequences of severe hypercalcemia, whether driven by RCC or other malignancies, include reduction in glomerular filtration rate, natriuresis and osmotic diuresis, nephrogenic diabetes insipidus, and direct tubular toxicity (6). This updated overview dedicated to the mitochondrial dysfunction and renal tubular injury in malignancy-associated hypercalcemia. We sought to consider a mechanistic framework for AKT in advanced renal cancer.

Search strategy

For this narrative 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 'malignancy', 'parathyroid hormone', 'hypercalcemia', 'parathyroid hormone–related peptide', 'renal cell carcinoma', 'acute kidney injury', 'mitochondria', 'oxidative stress' and 'glomerular filtration rate.'

Mitochondrial function in the kidney

Healthy mitochondria are essential for normal kidney function, and mitochondrial dysfunction has been linked to various inherited and acquired renal disorders. The kidneys are organs rich in mitochondria, which are imperative for meeting the high metabolic demands of the kidney and for sensing and responding to oxidative stress and inflammation caused by kidney injury (7). Mitochondrial dysfunction, particularly in renal tubular cells, is implicated in sepsis-induced renal tubular injury. In individuals with mitochondrial disorders, approximately half experience renal tubular dysfunction, though a smaller number develop overt kidney disease, suggesting a notable prevalence of renal involvement in mitochondrial cytopathies (8). Increases in intracellular and mitochondrial calcium content, often accompanying ischemic and toxic acute renal failure, have been proposed as mediators of renal tubular cell injury and dysfunction, although the exact mechanisms remain unclear (9). The previous study by Levi et al, on vitamin D-induced chronic hypercalcemia in rats showed that hypercalcemia leads to alterations in brush-border and basolateral membrane enzyme activity and lipid composition (10). This study found that, early cell injury and suggest a role for calcium in causing or predisposing to renal tubular cell injury (10). In acute settings, high serum calcium levels can induce necrosis of proximal tubular cells (11).

Kidney consequences of hypercalcemia

Hypercalcemia constricts the afferent arteriole and activates the calcium-sensing receptor (CaSR) in the thick ascending limb and collecting duct, leading to enhanced calcium reabsorption but also to salt and water wasting. This paradoxical combination enhanced calcium reabsorption with concurrent natriuresis and water loss, which promotes volume depletion, prerenal azotemia, and eventually ischemic tubular damage (12). Moreover, hypercalcemia induces metabolic alkalosis by increased bicarbonate reabsorption; alkalosis in turn augments distal tubular calcium reabsorption, further aggravating hypercalcemia and sustaining a vicious cycle of renal vasoconstriction, diuresis, and injury (13). Since hemodynamic and transport abnormalities account for a substantial component of AKI in hypercalcemic states, they do not fully explain the depth and persistence of tubular dysfunction seen in some patients with advanced RCC and malignancy-associated hypercalcemia (14,15). Experimental and translational data suggest that mitochondrial dysfunction within renal tubular epithelial cells forms a crucial mechanistic bridge between hypercalcemia and sustained tubular injury. Mitochondria are central to tubular cell energy metabolism, ion transport, and redox balance; while, these roles render them particularly vulnerable to calcium overload and oxidative stress (16). Increases in intracellular and mitochondrial calcium are well-described features of ischemic and toxic AKI, and chronic experimental hypercalcemia alters key biochemical properties of renal cortical plasma membranes and mitochondria in rats, implying that calcium excess itself predisposes tubular cells to damage (10).

In proximal tubule and thick ascending limb, the mitochondria generate ATP to sustain active transport by Na^+/K^+-ATPase and multiple cotransport systems. Indeed, proximal tubule and thick ascending limb are the nephron segments with highest oxidative metabolic demand (17). Meanwhile, hypercalcemia leads to increased filtered calcium load, across with volume depletion (18). Besides, the mismatch between oxygen supply and metabolic demand drives mitochondrial stress (19). Concurrent tumor-related inflammation and circulating cytokines further increase reactive oxygen species (ROS) generation and depress antioxidant defenses such as superoxide dismutase, setting up a redox-imbalanced environment (20). Then, ROS in excess damage mitochondrial DNA, disrupt oxidative phosphorylation complexes, and impair ATP generation, while also perpetuating a self-propagating loop of oxidative injury (21). Calcium overload within mitochondria is a decisive event in this context; since, high cytosolic calcium, driven by sustained hypercalcemia and CaSR-mediated signaling, enters mitochondria primarily by the mitochondrial calcium uniporter (22-24). At low to moderate levels, mitochondrial calcium can strengthen oxidative phosphorylation (25, 26); however, excessive mitochondrial calcium promotes opening of the mitochondrial permeability transition pore (mPTP), collapse of membrane potential, and release of pro-apoptotic factors (27). Experimental models of vitamin D–induced chronic hypercalcemia show increased mitochondrial calcium content in renal cortical tissue, along with structural and functional plasma membrane changes that are interpreted as markers of early tubular cell injury (10,28). Even when conventional mitochondrial enzyme activities appear preserved at early stages, such subtle biochemical and structural changes may prime tubular cells for exaggerated injury during superimposed ischemia or nephrotoxic exposure (29).

The interplay of systemic hypercalcemia, intrarenal hemodynamics, and mitochondrial dysfunction unfolds over multiple temporal scales (15). In the acute phase, severe hypercalcemia can precipitate abrupt AKI characterized by oliguria or non-oliguric renal failure, often accompanied by metabolic alkalosis and volume contraction (30). In these situations, prompt volume repletion and reduction of serum calcium, through saline diuresis, calcitonin, bisphosphonates, or denosumab frequently lead to partial or complete recovery of renal function, emphasizing the reversibility of the hemodynamic component (31). However, repeated episodes of hypercalcemic crises or persistent moderate hypercalcemia cause renal structural alterations (1).

In this condition, mitochondrial ROS not only impair oxidative phosphorylation but also promote epithelial-to-mesenchymal transition (EMT) and pro-fibrotic signaling in tubular cells (32, 33). The EMT is a common feature of chronic tubular injury and progression to end-stage renal disease (34). Through ROS-mediated signaling pathways, including activation of nuclear factor-κB and transforming growth factor-β/Smad cascades, injured tubular cells can adopt a more fibroblast-like phenotype, secreting extracellular matrix proteins and contributing to tubulointerstitial fibrosis and kidney failure (35,36). Over time, this structural remodeling diminishes nephron functional reserve, rendering the kidney more susceptible to acute insults such as recurrent hypercalcemic episodes, nephrotoxic chemotherapy, or sepsis (37,38). Therefore, mitochondrial dysfunction in hypercalcemia is both an acute effector of cell death and a long-term driver of chronic kidney damage (15).

In advanced RCC, additional factors converge on the mitochondria of renal tubular cells. Tumor-related systemic inflammation heightens oxidative stress via circulating cytokines and complement activation (39). Proteomic studies in autoimmune-related kidney disease demonstrate

that activation of complement and coagulation pathways in the tubules is tightly interlinked with mitochondrial respiratory chain damage, reduced ATP production, and increased ROS generation; although these data come from non-malignant conditions, the mechanistic links between complement activation, mitochondrial dysfunction, and tubular EMT are likely relevant to tumor-associated kidney injury as well (40). Previous studies detected that, RCC itself may alter systemic metabolic signaling, including derangements in lipid metabolism and hypoxia-inducible factor pathways, further modulating mitochondrial function in distant organs such as the kidney (41). In addition, therapies used for RCC such as tyrosine kinase inhibitors or immune checkpoint inhibitors can exert off-target renal mitochondrial toxicity in some patients, compounding the effects of hypercalcemia (15).

A fresh look at the hypercalcemia by RCC

The classical triad of hematuria, flank pain, and palpable mass is now less common as an initial presentation of RCC. Instead, many patients present with nonspecific symptoms and paraneoplastic syndromes such as hypercalcemia, weight loss, and anemia (42). Hypercalcemia in RCC is not merely an epiphenomenon but also as a marker of aggressive tumor biology and often advanced stage, particularly those with metastatic disease (43). In metastatic RCC cohorts, nephrectomy may temporarily ameliorate hypercalcemia in some patients, underscoring the causal link between tumor mass and calcium dysregulation (44); nonetheless, non-PTHrP mechanisms of hypercalcemia, including ectopic calcitriol production and cytokine-mediated bone resorption, appear more frequent than previously recognized (45). These observations highlight the heterogeneity of malignancy-associated hypercalcemia in RCC and the need to consider multiple upstream pathways when attempting to modulate downstream renal injury (43). A mechanistic framework for AKI in advanced renal cancer with malignancy-associated hypercalcemia can be conceptualized as a multi-tiered cascade (46). Previous authors determined that, RCC cells, especially in high-grade or metastatic lesions, secrete PTHrP, interleukins, notably IL-6, TNF-α, TGF-β, and possibly 1,25-dihydroxyvitamin D, across with stimulation of osteoclast activity by RANKL and other osteolytic mediators. These factors increase bone resorption and intestinal calcium absorption, elevating serum calcium and suppressing endogenous PTH (47). Likewise, elevated serum calcium causes afferent arteriolar vasoconstriction, decreased glomerular filtration rate, impaired concentrating ability by reduced collecting duct responsiveness to antidiuretic hormone, and salt-water diuresis (48). In addition, glomerular filtration rate declines abruptly, exacerbating uremic toxicity (49). In the next step, calcium crystals within tubules exacerbate obstruction and inflammation, creating vicious injury cycles characterized by cytokine release and leukocyte infiltration (50). Then, volume depletion and metabolic alkalosis develop; since, alkalosis enhances distal calcium reabsorption, further sustaining hypercalcemia and maintaining a cycle of vasoconstriction and diuresis. These changes precipitate prerenal azotemia and make the outer medulla, already borderline hypoxic, especially vulnerable to additional insults (30). In this milieu, when he filtered calcium load rises, requiring augmented reabsorption by proximal tubule and thick ascending limb cells through energy-dependent transporters and channels (51). In parallel, CaSR activation in the thick ascending limb alters NaCl and calcium handling, contributing to natriuresis while paradoxically promoting calcium conservation (52). Increased luminal calcium and altered membrane potentials facilitate calcium entry into tubular cells, raising cytosolic calcium concentrations (53). Accordingly, elevated cytosolic calcium enters mitochondria through the mitochondrial calcium uniporter. Initially, this may boost ATP production (54); however, persistence of high mitochondrial calcium and concurrent ROS generation produces oxidative damage to mitochondrial DNA and respiratory chain complexes (55, 56). Chronic experimental hypercalcemia is associated with increased mitochondrial calcium content and early biochemical changes in renal cortical plasma membranes and mitochondria, suggesting that calcium excess primes the tubule for injury even before overt enzyme dysfunction appears (57). As mitochondrial damage accumulates, oxidative phosphorylation becomes inefficient, ATP levels fall, and tubular cells cannot sustain high-energy reabsorptive processes (58). Opening of the mPTP leads to loss of mitochondrial membrane potential, release of cytochrome c and other pro-apoptotic mediators, and activation of apoptotic and necrotic pathways (59). Recent studies found that, ROS act as signaling molecules to induce EMT and fibrogenic programs, and with tubular cells contributing to interstitial matrix deposition and chronic tubulointerstitial scarring (60,61). This structural remodeling reduces nephron mass and predisposes patients to more severe and less reversible AKI upon subsequent hypercalcemic or hemodynamic challenges (15). Clinically, this integrated cascade manifests as AKI with variable degrees of oliguria, often with concurrent hypercalcemia, metabolic alkalosis, and evidence of volume contraction (15). In some RCC patients, correction of hypercalcemia through tumor-directed therapy leads to improved renal function, which underscores the causal linkage between tumor-secreted factors, hypercalcemia, and kidney injury (44,59). However, in others, particularly those with prolonged or recurrent hypercalcemia, intrinsic

tubular damage and mitochondrial dysfunction limit renal recovery even when calcium levels normalize. This framework also clarifies why malignancy-associated hypercalcemia in RCC correlates with poor prognosis beyond its role as an electrolyte disturbance (15). Hypercalcemia concurrently reflects aggressive tumor biology and drives organ dysfunction, especially renal and neurologic, which restricts therapeutic options, complicates fluid management, and increases susceptibility to treatment-related nephrotoxicity (62). Reduced renal function alters pharmacokinetics of systemic therapies, leading to dose reductions, delays, or contraindications, thereby indirectly influencing cancer outcomes (63). Furthermore, chronic kidney disease emerging from repeated AKI episodes and tubulointerstitial fibrosis further worsens overall survival and quality of life (64).

Conclusion

Malignancy-associated hypercalcemia frequently complicates advanced renal cancer, driving AKT through distinct mechanistic pathways involving cellular energy failure. Elevated serum calcium induces renal vasoconstriction and direct tubular toxicity, mediated by severe mitochondrial dysfunction. Excessive intracellular calcium overload disrupts mitochondrial membrane potential, triggering oxidative stress and impairing ATP production essential for cellular homeostasis. Specifically, calcium accumulation promotes the opening of the mitochondrial permeability transition pore, causing cytochrome c release and initiating apoptotic cascades. This bioenergetic failure compromises proximal tubular integrity, leading to widespread cell death through apoptosis and necrosis. Accordingly, glomerular filtration rate decreases suddenly, exacerbating uremic toxicity. Calcium crystals within tubules exacerbate obstruction and inflammation, creating vicious injury cycles characterized by cytokine release and leukocyte infiltration. This framework highlights mitochondria as critical hubs linking systemic hypercalcemia to tubular injury. Recognizing this pathway is imperative for developing targeted therapies beyond standard hydration and bisphosphonates. Novel therapeutic interventions might include mitochondrial antioxidants or permeability transition pore inhibitors to stabilize cellular energy metabolism. Actively protecting mitochondrial function could mitigate AKI severity, improving overall clinical outcomes in patients with advanced renal malignancies. Preserving renal function is fundamental for maintaining eligibility for systemic anticancer therapies, as dose reductions often compromise survival. Furthermore, preventing tubular necrosis reduces the risk of chronic kidney disease progression post-recovery. Eventually, addressing calcium-mediated mitochondrial toxicity offers a promising strategy to preserve renal function during aggressive cancer progression, potentially extending survival and quality of life in this vulnerable patient population, where renal compromise significantly limits therapeutic options and necessitates precise metabolic management

Authors' contribution

Conceptualization: Zahed Karimi and Naeem Nikpour.
Data cration: Karimov Zafar, Abdulloev Mukhriddin, and Elham Kebriyaei.
Investigation: Dilbar Kurbanova, Tolliboyeva Marjona, and Fariba Jafari Khabaz.
Supervision: All authors
Validation: Fariba Jafari Khabaz and Ahmadreza Maghsoudi.
Visualization: Elham Kebriyaei and Feruza Djalolova.
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.

Funding/Support

None.

References

1. Kanduri SR, Amarapurkar P, Hassanein M, Karam S, Velez JCQ, Jhaveri KD. Malignancy-Associated Hypercalcemia and Kidney Disease: Facts, Controversies, and Management. Kidney Med. 2026;8:101218. doi: 10.1016/j.xkme.2025.101218.
2. Novacescu D, Feciche BO, Cumpanas AA, Bardan R, Rusmir AV, Bitar YA, et al. Contemporary clinical definitions, differential diagnosis, and novel predictive tools for renal cell carcinoma. Biomedicines. 2022;10:2926. doi: 10.3390/biomedicines10112926.
3. Yano F, Sawada N, Tanaka N, Hikawa K, Hirose K, Ohtake Y, et al. PTHrP-Producing Renal Cell Carcinoma Presenting as Rapidly Progressive Cognitive Impairment: A Case Report. IJU Case Rep. 2026;9:e70142. doi: 10.1002/iju5.70142.
4. Lee M, Partridge NC. Parathyroid hormone signaling in bone and kidney. Curr Opin Nephrol Hypertens. 2009;18:298-

302. doi: 10.1097/MNH.0b013e32832c2264.
5. Chen SC, Kuo PL. Bone Metastasis from Renal Cell Carcinoma. Int J Mol Sci. 2016;17:987. doi: 10.3390/ijms17060987.
6. Capasso A, Benigni A, Capitanio U, Danesh FR, Di Marzo V, Gesualdo L, et al. Summary of the International Conference on Onco-Nephrology: an emerging field in medicine. Kidney Int. 2019;96:555-67. doi: 10.1016/j.kint.2019.04.043.
7. Emma F, Montini G, Parikh SM, Salviati L. Mitochondrial dysfunction in inherited renal disease and acute kidney injury. Nat Rev Nephrol. 2016;12:267-80. doi: 10.1038/nrneph.2015.214.
8. Arulkumaran N, Pollen S, Greco E, Courtneidge H, Hall AM, Duchen MR, et al. Renal Tubular Cell Mitochondrial Dysfunction Occurs Despite Preserved Renal Oxygen Delivery in Experimental Septic Acute Kidney Injury. Crit Care Med. 2018;46:e318-e25. doi: 10.1097/ccm.0000000000002937.
9. Cao M, Zhao X, Xia F, Shi M, Zhao D, Li L, et al. Mitochondrial dysfunction and metabolic reprogramming in acute kidney injury: mechanisms, therapeutic advances, and clinical challenges. Front Physiol. 2025;16:1623500. doi: 10.3389/fphys.2025.1623500.
10. Levi M, Molitoris BA, Burke TJ, Schrier RW, Simon FR. Effects of vitamin D-induced chronic hypercalcemia on rat renal cortical plasma membranes and mitochondria. Am J Physiol. 1987;252:F267-75. doi: 10.1152/ajprenal.1987.252.2.F267.
11. Simhadri PK, Leslie SW. Calcium Deposition and Other Renal Crystal Diseases. StatPearls. Treasure Island (FL): StatPearls Publishing LLC.; 2025.
12. Riccardi D, Brown EM. Physiology and pathophysiology of the calcium-sensing receptor in the kidney. Am J Physiol Renal Physiol. 2010;298:F485-99. doi: 10.1152/ajprenal.00608.2009.
13. Jeong JH, Bae EH. Hypercalcemia associated with acute kidney injury and metabolic alkalosis. Electrolyte Blood Press. 2010;8:92-4. doi: 10.5049/ebp.2010.8.2.92.
14. Giannakodimos I, Kaltsas A, Koumenis A, Mitakidi E, Adamos K, Deligiannis D, et al. Association between renal cell cancer and chronic kidney disease: an update on a never-healing wound. Biomedicines. 2025;1:26383. doi: 10.3390/biomedicines13112638.
15. Xu X, Zeng T, Chen S, Tian N, Zhang C, Chen Y, et al. Acute kidney injury: pathogenesis and therapeutic interventions. Mol Biomed. 2025;6:61. doi: 10.1186/s43556-025-00293-4.
16. Ho HJ, Shirakawa H. Oxidative Stress and Mitochondrial Dysfunction in Chronic Kidney Disease. Cells. 2022;12:88. doi: 10.3390/cells12010088.
17. Cheng YW, Cheng CJ. Mitochondrial bioenergetics: coupling of transport to tubular mitochondrial metabolism. Curr Opin Nephrol Hypertens. 2024;33:405-13. doi: 10.1097/mnh.0000000000000986.
18. Sadiq NM, Anastasopoulou C, Patel G, Badireddy M. Hypercalcemia. StatPearls. Treasure Island (FL): StatPearls Publishing LLC.; 2025.
19. Matuz-Mares D, González-Andrade M, Araiza-Villanueva MG, Vilchis-Landeros MM, Vázquez-Meza H. Mitochondrial Calcium: Effects of Its Imbalance in Disease. Antioxidants (Basel). 2022;11:801. doi: 10.3390/antiox11050801.
20. Kuo CL, Ponneri Babuharisankar A, Lin YC, Lien HW, Lo YK, Chou HY, et al. Mitochondrial oxidative stress in the tumor microenvironment and cancer immunoescape: foe or friend? J Biomed Sci. 2022;29:74. doi: 10.1186/s12929-022-00859-2.
21. Ježek J, Cooper KF, Strich R. Reactive Oxygen Species and Mitochondrial Dynamics: The Yin and Yang of Mitochondrial Dysfunction and Cancer Progression. Antioxidants (Basel). 2018;7:13. doi: 10.3390/antiox7010013.
22. Walkon LL, Strubbe-Rivera JO, Bazil JN. Calcium Overload and Mitochondrial Metabolism. Biomolecules. 2022;12:1891. doi: 10.3390/biom12121891.
23. Tian L, Andrews C, Yan Q, Yang JJ. Molecular regulation of calcium-sensing receptor (CaSR)-mediated signaling. Chronic Dis Transl Med. 2024;10:167-94. doi: 10.1002/cdt3.123.
24. Song J, Xiao L, Zhang Z, Wang Y, Kouis P, Rasmussen LJ, et al. Effects of reactive oxygen species and mitochondrial dysfunction on reproductive aging. Front Cell Dev Biol. 2024;12:1347286. doi: 10.3389/fcell.2024.1347286.
25. Bertero E, Maack C. Calcium Signaling and Reactive Oxygen Species in Mitochondria. Circ Res. 2018;122:1460-78. doi: 10.1161/circresaha.118.310082.
26. Glancy B, Willis WT, Chess DJ, Balaban RS. Effect of calcium on the oxidative phosphorylation cascade in skeletal muscle mitochondria. Biochemistry. 2013;52:2793-809. doi: 10.1021/bi3015983.
27. Endlicher R, Drahota Z, Štefková K, Červinková Z, Kučera O. The Mitochondrial Permeability Transition Pore-Current Knowledge of Its Structure, Function, and Regulation, and Optimized Methods for Evaluating Its Functional State. Cells. 2023;12:1273. doi: 10.3390/cells12091273.
28. Bhatia D, Capili A, Choi ME. Mitochondrial dysfunction in kidney injury, inflammation, and disease: Potential therapeutic approaches. Kidney Res Clin Pract. 2020;39:244-58. doi: 10.23876/j.krcp.20.082.
29. Fontecha-Barriuso M, Lopez-Diaz AM, Guerrero-Mauvecin J, Miguel V, Ramos AM, Sanchez-Niño MD, et al. Tubular Mitochondrial Dysfunction, Oxidative Stress, and Progression of Chronic Kidney Disease. Antioxidants (Basel). 2022;11:1356. doi: 10.3390/antiox11071356.
30. Aqeel F, Del Castillo J, Jaar BG, Hanouneh M. Hypercalcemia, Acute Kidney Injury, and Metabolic Alkalosis. Case Rep Nephrol. 2022;2022:1320259. doi: 10.1155/2022/1320259.
31. Calabrese V, Messina RM, Cernaro V, Farina A, Di Pietro Y, Gembillo G, et al. Hypercalcemia: A Practice Overview of Its Diagnosis and Causes. Kidney and Dialysis. 2025;5:7.
32. Braga PC, Alves MG, Rodrigues AS, Oliveira PF. Mitochondrial Pathophysiology on Chronic Kidney Disease. Int J Mol Sci. 2022;23:1776. doi: 10.3390/ijms23031776.
33. Jones CA, Hazlehurst LA. Role of Calcium Homeostasis in Modulating EMT in Cancer. Biomedicines. 2021;9:1200. doi: 10.3390/biomedicines9091200.
34. Kriz W, Kaissling B, Le Hir M. Epithelial-mesenchymal transition (EMT) in kidney fibrosis: fact or fantasy? J Clin Invest. 2011;121:468-74. doi: 10.1172/jci44595.
35. Niculae A, Gherghina ME, Peride I, Tiglis M, Nechita AM, Checherita IA. Pathway from Acute Kidney Injury to Chronic Kidney Disease: Molecules Involved in Renal Fibrosis. Int J Mol Sci. 2023;24:14019. doi: 10.3390/ijms241814019.
36. Tang PM, Zhang YY, Mak TS, Tang PC, Huang XR, Lan

HY. Transforming growth factor-β signalling in renal fibrosis: from Smads to non-coding RNAs. J Physiol. 2018;596:3493-503. doi: 10.1113/jp274492.
37. Turgut F, Awad AS, Abdel-Rahman EM. Acute Kidney Injury: Medical Causes and Pathogenesis. J Clin Med. 2023;12:375. doi: 10.3390/jcm12010375.
38. Goyal A, Daneshpajouhnejad P, Hashmi MF, Bashir K. Acute Kidney Injury. StatPearls. Treasure Island (FL): StatPearls Publishing LLC.; 2025.
39. Kruk L, Mamtimin M, Braun A, Anders HJ, Andrassy J, Gudermann T, et al. Inflammatory networks in renal cell carcinoma. Cancers (Basel). 2023;15:2212. doi: 10.3390/cancers15082212.
40. Xiao M, Chi X, Zhu X, Xu Z, Zou Y, Peng Y, et al. Proteomic analysis of laser captured tubular tissues reveals complement activation and mitochondrial dysfunction in autoimmune related kidney diseases. Sci Rep. 2024;14:19311. doi: 10.1038/s41598-024-70209-9.
41. Yang J, Miao D, Li X, Zhao C, Tan D, Wu S, et al. Emerging roles of metabolic biomarkers in renal cell carcinoma: from molecular mechanisms to clinical implications. Front Cell Dev Biol. 2025;13:1664292. doi: 10.3389/fcell.2025.1664292.
42. Palapattu GS, Kristo B, Rajfer J. Paraneoplastic syndromes in urologic malignancy: the many faces of renal cell carcinoma. Rev Urol. 2002;4:163-70.
43. Subedi BK, Modi S, Gautam N, Upadhyay A, Baek P, Bitetto D. Severe hypercalcemia as the initial presentation of renal cell carcinoma: a diagnostic case report. Ann Med Surg (Lond). 2025;87:3016-22. doi: 10.1097/ms9.0000000000003252.
44. Walther MM, Patel B, Choyke PL, Lubensky IA, Vocke CD, Harris C, et al. Hypercalcemia in patients with metastatic renal cell carcinoma: effect of nephrectomy and metabolic evaluation. J Urol. 1997;158:733-9. doi: 10.1097/00005392-199709000-00011.
45. Chukir T, Liu Y, Hoffman K, Bilezikian JP, Farooki A. Calcitriol Elevation Is Associated with a Higher Risk of Refractory Hypercalcemia of Malignancy in Solid Tumors. J Clin Endocrinol Metab. 2020;105:e1115-23. doi: 10.1210/clinem/dgz278.
46. Habas E, Akbar R, Farfar K, Arrayes N, Habas A, Rayani A, et al. Malignancy diseases and kidneys: A nephrologist prospect and updated review. Medicine (Baltimore). 2023;102:e33505. doi: 10.1097/md.0000000000033505.
47. Paragliola RM, Torino F, Barnabei A, Iannantuono GM, Corsello A, Locantore P, et al. Bone metabolism effects of medical therapy in advanced renal cell carcinoma. Cancers (Basel). 2023;15:529. doi: 10.3390/cancers15020529.
48. Alexander RT, Dimke H. Effect of diuretics on renal tubular transport of calcium and magnesium. Am J Physiol Renal Physiol. 2017;312:F998-f1015. doi: 10.1152/ajprenal.00032.2017.
49. Chao CT, Lin SH. Uremic Toxins and Frailty in Patients with Chronic Kidney Disease: A Molecular Insight. Int J Mol Sci. 2021;22:6270. doi: 10.3390/ijms22126270.
50. Mulay SR, Anders HJ. Crystal nephropathies: mechanisms of crystal-induced kidney injury. Nat Rev Nephrol. 2017;13:226-40. doi: 10.1038/nrneph.2017.10.
51. Hanna RM, Ahdoot RS, Kalantar-Zadeh K, Ghobry L, Kurtz I. Calcium Transport in the Kidney and Disease Processes. Front Endocrinol (Lausanne). 2021;12:762130. doi: 10.3389/fendo.2021.762130.
52. Riccardi D, Valenti G. Localization and function of the renal calcium-sensing receptor. Nat Rev Nephrol. 2016;12:414-25. doi: 10.1038/nrneph.2016.59.
53. Staruschenko A, Alexander RT, Caplan MJ, Ilatovskaya DV. Calcium signalling and transport in the kidney. Nat Rev Nephrol. 2024;20:541-55. doi: 10.1038/s41581-024-00835-z.
54. Boyman L, Karbowski M, Lederer WJ. Regulation of Mitochondrial ATP Production: Ca(2+) Signaling and Quality Control. Trends Mol Med. 2020;26:21-39. doi: 10.1016/j.molmed.2019.10.007.
55. Adam-Vizi V, Starkov AA. Calcium and mitochondrial reactive oxygen species generation: how to read the facts. J Alzheimers Dis. 2010;20 Suppl 2:S413-26. doi: 10.3233/jad-2010-100465.
56. Guo C, Sun L, Chen X, Zhang D. Oxidative stress, mitochondrial damage and neurodegenerative diseases. Neural Regen Res. 2013;8:2003-14. doi: 10.3969/j.issn.1673-5374.2013.21.009.
57. Hoogstraten CA, Hoenderop JG, de Baaij JHF. Mitochondrial Dysfunction in Kidney Tubulopathies. Annu Rev Physiol. 2024;86:379-403. doi: 10.1146/annurev-physiol-042222-025000.
58. Pavlović N, Križanac M, Kumrić M, Vukojević K, Božić J. Mitochondrial Dysfunction: The Silent Catalyst of Kidney Disease Progression. Cells. 2025;14:794. doi: 10.3390/cells14110794.
59. Kinnally KW, Peixoto PM, Ryu SY, Dejean LM. Is mPTP the gatekeeper for necrosis, apoptosis, or both? Biochim Biophys Acta. 2011;1813:616-22. doi: 10.1016/j.bbamcr.2010.09.013.
60. Kim KP, Williams CE, Lemmon CA. Cell-Matrix Interactions in Renal Fibrosis. Kidney Dial. 2022;2:607-24. doi: 10.3390/kidneydial2040055.
61. Liu Y. Cellular and molecular mechanisms of renal fibrosis. Nat Rev Nephrol. 2011;7:684-96. doi: 10.1038/nrneph.2011.149.
62. Bartkiewicz P, Kunachowicz D, Filipski M, Stebel A, Ligoda J, Rembiałkowska N. Hypercalcemia in Cancer: Causes, Effects, and Treatment Strategies. Cells. 2024;13:1051. doi: 10.3390/cells13121051.
63. Poole C, Gardiner J, Twelves C, Johnston P, Harper P, Cassidy J, et al. Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. Cancer Chemother Pharmacol. 2002;49:225-34. doi: 10.1007/s00280-001-0408-0.
64. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371:58-66. doi: 10.1056/NEJMra1214243.