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Recurrent dehydration and chronic kidney disease; molecular pathways linking osmotic stress, tubular injury and fibrotic progression

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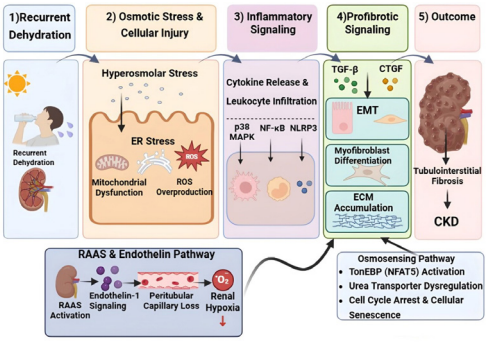
ABSTRACT



Recurrent dehydration has detected as a significant, modifiable risk factor for the development and progression of chronic kidney disease, particularly in populations exposed to occupational heat stress or limited fluid access. This overview sought to consider current findings on the molecular pathways linking episodic volume depletion to sustained renal dysfunction, emphasizing osmotic stress as the primary catalyst for tubular epithelial injury. Repeated hyperosmolar insults disrupt cellular homeostasis, provoking mitochondrial dysfunction, endoplasmic reticulum stress, and excessive reactive oxygen species production. These perturbations activate conserved signaling cascades, notably p38 MAPK, NF-κB, and the NLRP3 inflammasome, which drive pro-inflammatory cytokine release and sustained leukocyte infiltration. Concurrently, osmotic stress potently upregulates transforming growth factor-beta and connective tissue growth factor, precipitating epithelial-to-mesenchymal transition and myofibroblast differentiation. The consequent extracellular matrix accumulation, compounded by defective autophagy and maladaptive proliferative responses, establishes a self-sustaining loop of tubulointerstitial fibrosis. Recurrent dehydration further amplifies intrarenal renin-angiotensin-aldosterone system activity and endothelin-1 signaling, accelerating peritubular capillary loss and hypoxia-driven fibrogenesis. Recent data further implicate urea transporter dysregulation and tonicity-responsive enhancer-binding protein activation in exacerbating tubular cell cycle arrest and cellular senescence. Interpretation of these interconnected molecular networks reveals promising therapeutic targets that could interrupt the transition from acute osmotic injury to irreversible architectural damage. Finally, integrating mechanistic insights with clinical epidemiology reinforces the urgent need for evidence-based hydration protocols and novel antifibrotic strategies to mitigate the rising global incidence of dehydration-related chronic kidney disease.

Review

Introduction

The growing recognition of recurrent dehydration as a silent yet potent driver of chronic kidney disease (CKD) has shifted clinical and scientific attention toward the underlying molecular cascades that transform transient volume depletion into irreversible renal parenchymal scarring (1,2). Unlike acute, severe hypovolemic episodes that precipitate overt acute kidney injury, recurrent subclinical dehydration operates through insidious, cumulative mechanisms that progressively erode renal homeostasis (1,3). This form of chronic fluid deficit is particularly prevalent in occupations characterized by sustained heat exposure and limited hydration, agricultural laborers, and populations in arid climates, where repeated daily cycles of mild to moderate volume contraction become embedded in the physiological baseline (4,5). The kidney, uniquely adapted to concentrate urine and preserve systemic osmolarity,

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Implication for health policy/practice/research/medical education:
Recurrent dehydration initiates a maladaptive cascade that accelerates chronic kidney disease by exposing the renal medulla to sustained hyperosmolar stress. This osmotic imbalance activates TonEBP/NFAT5 and stress-responsive kinases, driving excessive reactive oxygen species production and mitochondrial dysfunction in renal tubular epithelial cells. Persistent osmotic and oxidative insults trigger kidney tubular cell apoptosis, necrosis, and impaired regenerative capacity, creating a proinflammatory microenvironment. Damaged tubules subsequently overexpress transforming growth factor-β1, connective tissue growth factor, and pro-fibrotic cytokine networks, which promote epithelial-to-mesenchymal transition and sustained myofibroblast differentiation. Concurrently, chronic medullary hypoxia and renin-angiotensin system activation amplify extracellular matrix deposition while suppressing degradative metalloproteinase activity. Over time, these intertwined molecular pathways convert transient osmotic stress into irreversible interstitial fibrosis, progressively compromising nephron function and establishing a self-perpetuating cycle that drives the clinical transition from adaptive physiology to end-stage chronic kidney disease.

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is paradoxically the organ most vulnerable to the very stresses it is designed to manage (6,7). When dehydration recurs at frequencies that outpace reparative capacity, the renal microenvironment undergoes sustained osmotic and hypoxic perturbations that initiate a self-perpetuating cycle of tubular dysfunction, maladaptive signaling, and extracellular matrix deposition (1). At the molecular level, this transition hinges on the interplay between osmoadaptive responses, cellular stress pathways, inflammatory signaling, and fibrogenic networks that collectively reprogram renal architecture (1). Here we therefore sought to discuss on the recurrent dehydration and CKD by considering molecular pathways linking osmotic stress, tubular injury and fibrotic progression.

Search strategy

A literature search was conducted using the following electronic databases: PubMed, Google Scholar, DOAJ, Web of Science, EBSCO, Scopus, and Embase. The search strategy employed relevant keywords, including dehydration, acute kidney injury, chronic kidney disease, inflammation, fibrosis, reactive oxygen species, proximal tubule, acute tubular injury, mitochondrial dysfunction, tubulointerstitial fibrosis, tubular epithelial injury, and chronic hypoxia.

Dehydration-associated CKD

Central to the renal response to recurrent dehydration is the dynamic alteration of medullary osmolarity (8). Under normal physiological conditions, the renal medulla maintains a steep osmotic gradient driven by active solute transport in the thick ascending limb and urea recycling in the collecting duct (9). Dehydration amplifies this gradient as the kidney conserves water through intensified antidiuretic hormone signaling and reduced perfusion (1). While short-term hyperosmolarity is managed through the activation of tonicity-responsive enhancer binding protein, also known as NFAT5, which orchestrates the transcription of osmoprotective genes such as aldose reductase, betaine-GABA transporter, and sodium-myoinositol cotransporter, chronic or fluctuating hyperosmotic stress overwhelms this adaptive machinery (10,11). Persistent activation of NFAT5 leads to sustained transcriptional activity that, beyond a critical threshold, promotes pro-inflammatory and pro-fibrotic gene expression rather than cytoprotection (12). The osmotic imbalance also directly compromises tight junction integrity and alters paracellular permeability, facilitating back-leak of filtrate and exacerbating tubular workload (13,14). Furthermore, the concentrated medullary environment intensifies oxidative stress by enhancing the auto-oxidation of solutes and impairing antioxidant enzyme kinetics, particularly superoxide dismutase and catalase, which are sensitive to ionic strength fluctuations (15,16). This osmotic stress does not act in isolation; it converges with hypoxia to create a synergistic injury milieu that fundamentally alters tubular cell metabolism and survival signaling (17).

Role of hypoxia in dehydration-induced renal injury

Hypoxia detected as a critical co-factor in dehydration-induced renal injury due to the anatomical and hemodynamic features of the renal medulla, which already operates near the threshold of oxygen tension under baseline conditions (1,18,19). Recurrent volume contraction reduces renal blood flow, disproportionately affecting the outer medulla where oxygen supply-demand balance is most precarious (20). The resulting chronic hypoxia stabilizes hypoxia-inducible factor-1α (HIF-1α), a master transcriptional regulator that initially promotes erythropoiesis, angiogenesis, and glycolytic adaptation (21). However, prolonged HIF-1α activation in the context of recurrent dehydration drives pathological remodeling by upregulating vascular endothelial growth factor in a dysregulated manner, leading to aberrant microvascular architecture, increased permeability, and peritubular capillary rarefaction (22,23). The loss of capillary density further entrenches hypoxia, establishing a vicious cycle that primes tubular epithelial cells for injury (24). Concurrently, HIF-1α interacts with NF-κB to amplify inflammatory cytokine production, including interleukin-6 and tumor necrosis factor-alpha, which

recruit immune cells and activate resident fibroblasts (25,26). The metabolic consequences of sustained hypoxia are equally profound, as tubular cells, particularly in the proximal segment, rely heavily on fatty acid oxidation for ATP generation (27). Hypoxia suppresses peroxisome proliferator-activated receptor alpha signaling and downregulates carnitine palmitoyltransferase-1, shifting energy metabolism toward less efficient glycolysis (28). This metabolic reprogramming not only depletes cellular ATP reserves but also promotes lipid accumulation, endoplasmic reticulum stress, and the generation of reactive oxygen species through uncoupled mitochondrial electron transport (29,30).

Impact of recurrent dehydration on proximal tubule

The proximal tubule, which is responsible for the bulk of solute and water reabsorption, bears the effect of recurrent dehydration-induced stress due to its high metabolic demand and direct exposure to concentrated filtrate (31). Osmotic and hypoxic insults trigger endoplasmic reticulum stress through the accumulation of misfolded proteins and disrupted calcium homeostasis, activating the unfolded protein response (32). While transient unfolded protein response activation by PERK, IRE1α, and ATF6 pathways aims to restore proteostasis, chronic stimulation leads to CHOP-mediated apoptosis and sustained IRE1α-dependent JNK activation, which promotes inflammatory signaling and cellular senescence (33). Mitochondrial dysfunction compounds this injury, as recurrent dehydration impairs mitophagy through downregulation of PINK1 and Parkin, allowing damaged mitochondria to persist and leak pro-apoptotic factors such as cytochrome c and apoptosis-inducing factor (34,35). The resulting oxidative burst damages DNA, lipids, and proteins, activating poly(ADP-ribose) polymerase and depleting NAD+ pools, which further compromises sirtuin-mediated stress resistance and amplifies cellular vulnerability (36). In parallel, recurrent hypovolemia alters the expression and activity of ferroptosis regulators, with decreased glutathione peroxidase 4 and increased acyl-CoA synthetase long-chain family member 4 sensitizing tubular cells to iron-dependent lipid peroxidation (37,38). This form of regulated necrosis releases damage-associated molecular patterns that activate pattern recognition receptors and perpetuate sterile inflammation, bridging acute tubular injury to chronic inflammatory remodeling (39).

Focus on inflammatory signaling pathways

Inflammatory signaling pathways serve as critical intermediaries between tubular stress and fibrotic progression in the setting of recurrent dehydration (40). The NLRP3 inflammasome, a multiprotein complex activated by ionic imbalance, mitochondrial ROS (reactive oxygen species), and lysosomal destabilization, plays a central role in this transition (41). Repeated osmotic fluctuations and hypoxic stress promote potassium efflux and mitochondrial dysfunction, which converge to trigger NLRP3 assembly and caspase-1 activation (42,43). This leads to the maturation and secretion of interleukin-1β and interleukin-18, cytokines that amplify local inflammation, recruit macrophages, and polarize them toward a pro-fibrotic M2 phenotype (44). Concurrently, nuclear factor kappa-B is persistently activated through toll-like receptor signaling and reactive oxygen species-mediated IκB (inhibitor of kappa B) degradation, driving the transcription of chemokines such as CCL2 and CXCL10 that sustain leukocyte infiltration (45,46). The inflammatory milieu also upregulates inducible nitric oxide synthase, generating peroxynitrite that nitrates mitochondrial proteins and further impairs oxidative phosphorylation (16). Importantly, inflammation and fibrosis are not sequential but interwoven processes; cytokines like transforming growth factor-beta are produced by both immune cells and stressed epithelial cells, acting in autocrine and paracrine fashion to initiate matrix-producing programs (47,48). The recurrent nature of dehydration ensures that these inflammatory episodes never fully resolve, instead accumulating subclinical damage that progressively tips the balance from repair to scarring (1,49).

Role of renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system and vasopressin signaling represent two neurohormonal axes that are chronically upregulated during recurrent dehydration and exert profound mechanistic influence on renal injury and fibrosis (50,51). Besides, volume contraction stimulates renin release, leading to increased angiotensin II production, which binds to AT1 receptors on tubular epithelial cells, mesangial cells and fibroblasts (52). Angiotensin II signaling activates NADPH oxidase isoforms, particularly NOX4, generating superoxide that oxidizes lipids and activates redox-sensitive kinases such as p38 MAPK and JNK (53). These kinases phosphorylate transcription factors that upregulate fibrotic mediators, including connective tissue growth factor and plasminogen activator inhibitor-1, while simultaneously suppressing matrix metalloproteinases through tissue inhibitor of metalloproteinase induction (53,54). Angiotensin II also promotes epithelial-mesenchymal transition by down-regulating E-cadherin and upregulating vimentin and α-smooth muscle actin, endowing tubular cells with migratory and matrix-synthetic properties (55,56). In parallel, dehydration stimulates arginine vasopressin release, which acts on V2 receptors in the collecting duct to increase cyclic AMP and promote aquaporin-2 insertion (57,58). Though this mechanism conserves water acutely, chronic vasopressin type 2 (V2) receptor activation induces hyperfiltration in surviving nephrons, increases glomerular capillary pressure, and promotes podocyte stress (57,58). Furthermore, vasopressin signaling

intersects with TGF-β (transforming growth factor-β) pathways through cAMP-responsive element binding protein phosphorylation, synergistically enhancing collagen synthesis and myofibroblast differentiation (59,60). The combined effects of angiotensin II and vasopressin create a hemodynamic and molecular environment that favors progressive parenchymal remodeling over functional recovery (61,62).

From tubular injury to fibrosis

As tubular injury accumulates, the kidney's reparative capacity becomes increasingly maladaptive, culminating in the activation of fibrogenic networks that replace functional tissue with extracellular matrix (63). In the meantime, transforming growth factor-β remains the cornerstone of this process, operating through canonical Smad2/3 phosphorylation and non-canonical pathways involving TAK1, PI3K/Akt, and ERK (64). In recurrent dehydration, TGF-β is persistently activated through integrin-mediated latency-associated peptide cleavage, thrombospondin-1 release, and reactive oxygen species-dependent conformational changes (65,66). The resulting Smad signaling complex translocates to the nucleus and drives the transcription of collagen types I, and III, fibronectin, and also α-smooth muscle actin, while simultaneously inhibiting proteolytic enzymes that would otherwise degrade excess matrix (67). Meanwhile, Wnt/β-catenin signaling acts as a critical amplifier of TGF-β effects, as tubular injury stabilizes β-catenin through GSK-3β inhibition and promotes its nuclear translocation, where it interacts with TCF/LEF transcription factors to upregulate fibrotic and proliferative genes (68). The crosstalk between Wnt and TGF-β pathways establishes a self-reinforcing loop that resists resolution and locks the kidney into a fibrotic trajectory (69). Additionally, mechanical stress from altered tubular flow and interstitial pressure activates yes-associated protein and transcriptional coactivator with PDZ-binding motif, which translocate to the nucleus and synergize with Smad complexes to enhance matrix gene expression (70). The extracellular matrix itself becomes progressively cross-linked through lysyl oxidase activity and advanced glycation end-product formation, reducing tissue compliance and further impairing perfusion, thereby closing a pathophysiological feedback loop that sustains chronic injury (71,72). Cellular senescence and epigenetic reprogramming represent new mechanistic layers that explain the irreversibility of dehydration-associated fibrotic progression (73,74). Repeated cycles of osmotic and hypoxic stress induce DNA damage and telomere attrition in tubular epithelial cells, triggering p53 and p16INK4a-dependent cell cycle arrest (24,75). Senescent cells do not merely cease dividing; since, they adopt a senescence-associated secretory phenotype characterized by the sustained release of interleukins, chemokines, growth factors, and matrix metalloproteinases that remodel the microenvironment and activate neighboring fibroblasts (76). This paracrine signaling field amplifies inflammation and fibrosis beyond the initially injured nephron segments (76). Epigenetic modifications lock these phenotypic changes into long-term memory (77). In fibrotic disease contexts, TGF-β–driven upregulation of DNA methyltransferases (DNMT1/3a) induces promoter hypermethylation and transcriptional silencing of renoprotective genes such as Klotho and BMP-7 (78). Concurrently, histone deacetylases repress antifibrotic transcription factors through two complementary mechanisms; (i) histone deacetylation-mediated chromatin condensation at target gene promoters (79), and (ii) direct deacetylation of non-histone substrates including Nrf2, Krüppel-like factors, and Sp1, thereby impairing their DNA-binding affinity or transcriptional activity (80). On the other hand, microRNAs further fine-tune this landscape, with miR-21 downregulating PTEN and SMAD7 to enhance TGF-β signaling, and miR-29 suppression relieving inhibition on collagen and elastin synthesis (81). The cumulative effect is a transcriptional and post-transcriptional program that favors matrix accumulation, impairs regeneration, and reduces cellular plasticity (82). Importantly, these epigenetic alterations can persist even after hydration status is restored, explaining why recurrent dehydration leaves a lasting footprint on renal architecture and why early intervention is critical to prevent irreversible commitment to fibrotic pathways (1,83). The integration of these molecular pathways reveals a coherent mechanistic narrative in which recurrent dehydration initiates a cascade of osmotic, hypoxic, and metabolic stresses that overwhelm tubular adaptive capacity, trigger inflammatory and fibrogenic signaling, and ultimately remodel the renal parenchyma through maladaptive repair and epigenetic fixation (1,84,85). What distinguishes this pathway from classical ischemic nephropathy is the chronicity, fluctuation, and subclinical nature of the insult, which prevents full resolution between episodes and instead allows molecular damage to accumulate incrementally (86,87). The kidney's remarkable ability to concentrate urine and preserve volume becomes its liability when the stressor is recurrent, as the very mechanisms designed for short-term survival mediate long-term structural compromise (88). Osmotic stress primes cells for injury through NFAT5 (nuclear factor of activated t cells 5) overactivation and antioxidant depletion, hypoxia reprograms metabolism and stabilizes HIF-1α-driven inflammatory networks, mitochondrial dysfunction and ferroptosis execute regulated cell death, and neurohormonal axes like RAAS (renin-angiotensin-aldosterone) and vasopressin translate hemodynamic changes into molecular fibrogenic signals (12,89-91). These processes converge on the activation of myofibroblasts, whether through epithelial-mesenchymal transition, pericyte detachment, or fibroblast proliferation, and are sustained by TGF-β, Wnt/β-catenin, and YAP/

TAZ signaling hubs (92). The extracellular matrix that replaces functional tissue is not inert scar but a dynamic signaling compartment that perpetuates hypoxia, stiffens the microenvironment, and locks cells into senescent or profibrotic states (82). Identification of the continuum provides a framework for targeting specific nodes along the pathway, such as osmoadaptive modulators, mitochondrial protectants, inflammasome inhibitors, antifibrotic biologics, or epigenetic editors, before the transition to established CKD becomes irreversible (8,93,94). Future research must focus on delineating the threshold of recurrent dehydration that shifts adaptive responses toward pathology, identifying early molecular biomarkers of maladaptive repair, and developing interventions that enhance renal resilience without compromising physiological concentrating ability (1,95). Only by dissecting the precise molecular choreography linking osmotic stress to tubular injury and fibrotic progression can we develop targeted strategies to halt the silent progression of dehydration-associated CKD and preserve renal function in vulnerable populations worldwide (1,85).

Conclusion

Recurrent dehydration emerges as a critical, yet often overlooked, driver of CKD, establishing a pathophysiological cascade that bridges transient osmotic stress to irreversible fibrotic remodeling. Persistent hypovolemia and hyperosmolarity impose profound cellular strain on renal tubular epithelial cells, triggering adaptive survival responses that, when chronically activated, transition into maladaptive signaling. At the molecular level, sustained osmotic stress upregulates tonicity-responsive enhancer-binding protein and activates stress kinases such as p38 MAPK and JNK, which included to pro-inflammatory transcription factors like NF-κB. This cascade amplifies the release of cytokines and chemokines, recruiting immune cells and fostering a microenvironment conducive to tubular atrophy and interstitial inflammation. Concurrently, hypoxia-inducible factors and oxidative stress pathways synergize to promote epithelial-to-mesenchymal transition, while transforming growth factor-β and connective tissue growth factor orchestrate myofibroblast differentiation and excessive extracellular matrix deposition. Over time, these interconnected mechanisms erode renal architecture, impair microvascular perfusion, and lock the kidney into a self-perpetuating cycle of injury and fibrosis. Moreover, epidemiological evidence increasingly corroborates this biological plausibility, particularly in occupational and geographical contexts where heat exposure and limited water access exist. Recognizing dehydration as a modifiable risk factor underscores the urgent need for integrated preventive strategies, including targeted hydration protocols and early biomarker surveillance. Future studies should delineate the precise threshold of osmotic insult required to initiate irreversible damage and evaluate therapeutic interventions that interrupt key nodes within this pathogenic network. Finally, mitigating recurrent volume depletion represents a pragmatic and physiologically grounded approach to halting the early stages of CKD progression and preserving long-term renal function.

Authors' contribution

Conceptualization: Eleonora Tashkenbaeva, Maftuna Abdulloeva.
Data curation: Sabokhat Tuychieva, Sadriddin Mukhtarov.
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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, double publication) have been completely observed by the authors.

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