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Review Article

The dual role of ion channels in diabetic kidney disease: a translational paradigm for biomarkers and target discovery - reviews and prospects

Xiaojing Xiong[1*], Bao Yan[1*], Bi Ke[2*], Chen Wang[1], Xiuyuan Feng[2], Hua Yan[2], Wenfeng Wang[1], Guang Xu[2]

[1]Department of Cardiology, Wuhan Asia General Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, China; [2]Department of Cardiology, Ezhou Central Hospital, Ezhou, Hubei, China. [*]Equal contributors.

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Abstract: The clinical heterogeneity of diabetic kidney disease (DKD) poses a major challenge to current treatment strategies. This review proposes a novel translational paradigm: viewing ion channels as dual-function entities that serve both as pathogenic mediators and as rich sources of clinically actionable biomarkers. We systematically elucidate how hyperglycemia, oxidative stress, and inflammation disrupt sodium, calcium, potassium, and chloride channel networks through interconnected pathways such as AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR), NLR family pyrin domain containing 3 (NLRP3), and PIEZO1. These disruptions not only drive renal injury but also generate a cascade of detectable molecular signals - from genomic variations and epigenetic changes to circulating protein fragments and exosomal non-coding RNAs. We review these multi-level biomarker sources and their detection platforms, including cutting-edge, minimally invasive technologies such as urinary cell-free DNA (cfDNA) methylation profiling and artificial intelligence (AI)-driven multi-omics integration. Crucially, we detail how these "channelopathy fingerprints" can be translated into clinical tools for molecular endotyping, predicting and monitoring treatment responses to established (sodium-glucose cotransporter 2 (SGLT2) inhibitors, finerenone) and emerging (transient receptor potential canonical 6 (TRPC6) inhibitors) therapies, and optimizing clinical trial designs through biomarker-driven enrichment strategies. Finally, we propose a phased, multi-stakeholder roadmap from biomarker discovery to clinical integration, aiming to shift DKD management from a "one-size-fits-all" approach to individualized precision therapy.

Keywords: Diabetic kidney disease, ion channels biomarkers, precision medicine, single-cell omics, artificial intelligence, SGLT2, TRP channels

Introduction

Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease (ESRD) worldwide [1]. Although therapies such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and the novel non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone have significantly improved patient prognosis, substantial interindividual variability in therapeutic response persists, with a significant subset of patients continuing to experience disease progression [2, 3]. This therapeutic ceiling underscores the inherent pathophysiological heterogeneity of DKD and highlights the limitations of relying on traditional, late-stage indicators like proteinuria and estimated glomerular filtration rate (eGFR) to guide precision therapy [4, 5].

Ion channels in the kidney play central roles in maintaining water-electrolyte balance, glomerular filtration, and cellular signaling [6, 7]. Substantial evidence indicates that in the DKD milieu, various ion channels - including SGLT2, the epithelial sodium channel (ENaC), transient receptor potential canonical 6 (TRPC6), and the mechanosensitive channel PIEZO1 - undergo specific dysregulation in expression, localization, and function, directly contributing to key pathological processes such as glomerular hypertension, podocyte injury, tubular dysfunction, and interstitial fibrosis [8-11]. While their

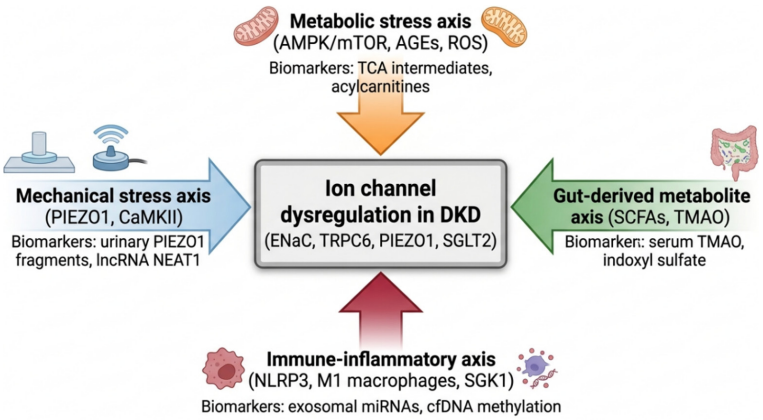

Figure 1. Multi-axis pathogenic mechanisms leading to ion channel dysregulation in DKD. A schematic illustrating how metabolic stress, immune-inflammatory activation, mechanical stress, and gut-derived metabolites converge to disrupt renal ion channel function. Key channels affected include ENaC, TRPC6, PIEZO1, and SGLT2. Each axis generates specific molecular signals that serve as potential biomarkers.

role as therapeutic targets has been extensively reviewed [12], this manuscript introduces a critical and clinically-oriented expansion of that perspective.

We propose a novel paradigm that focuses on the dual role of ion channels. Beyond being pathogenic effectors, we argue that the very process of channel dysfunction generates a wealth of quantifiable molecular signals - "channelopathy fingerprints" - detectable in blood and urine. These signals, ranging from specific gene variants and epigenetic marks to circulating protein fragments and exosomal microRNAs (miRNAs), can be harnessed as a new class of biomarkers [13-17]. This framework directly addresses a core clinical challenge: bridging the gap between our deep molecular understanding of DKD and the relatively blunt instruments available for patient management.

This review aims to systematically elaborate on this "dual-perspective" framework. We will: (1) summarize how key pathogenic pathways in DKD converge on the ion channel network and generate specific biomarker signals; (2) categorize and evaluate different types of ion channel-related biomarkers and their detection platforms; (3) discuss translational strategies for using these biomarkers to guide patient stratification, optimize existing therapies, and accelerate new drug development; and (4) analyze current challenges and propose a clinical integration roadmap.

Molecular mechanisms of DKD: from systemic disturbance to ion channel-specific injury

The pathological progression of DKD is triggered by systemic metabolic disturbances, leading to dysregulation of the local renal microenvironment. A core manifestation is the functional remodeling and injury of ion channel networks [18, 19]. Hyperglycemia induces systemic and local metabolic-inflammatory-biomechanical axis imbalances that precisely target and reshape key renal ion transporters [20].

At the molecular level, this process involves the synergistic action of several intertwined pathological axes: the metabolic stress axis, the immune-inflammatory axis, the mechanical stress axis, and the systemic metabolite communication axis (**Figure 1**).

The Metabolic Stress Axis is characterized by an imbalance between the intracellular energy sensor AMP-activated protein kinase (AMPK) and the synthetic regulator mammalian target of rapamycin complex 1 (mTORC1). This imbalance directly regulates the gene expression of calcium channels such as TRPC6, converting cellular energy crises into calcium signaling disorders [21, 22]. Concurrently, advanced glycation end products (AGEs) and reactive oxygen species (ROS) activate protein kinase C (PKC), modifying channel proteins like ENaC and altering their gating properties [23].

The Immune-Inflammatory Axis manifests as a chronic low-grade inflammatory state maintained by NLR family pyrin domain containing 3 (NLRP3) inflammasome activation and M1 macrophage polarization [24-30]. Cytokines released (e.g., interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α)) upregulate ENaC expression and activity via serum/glucocorticoid-regulated kinase 1 (SGK1), directly linking inflammation to sodium retention and hyper-

Table 1. Multi-level sources and detection platforms for ion channel-related biomarkers in DKD

Biomarker Level	Example Sources	Detection Technologies	Potential Clinical Utility
Genomic	SLC5A2, SCNN1 variants	SNP array, NGS, PRS calculation	Risk prediction, pharmacogenomics
Transcriptomic/Epigenetic	scRNA-seq data, DNA methylation, urinary cfDNA methylation	scRNA-seq, methylation arrays, RNA-seq, targeted bisulfite sequencing	Molecular subtyping, disease activity, dynamic monitoring
Proteomic	Urinary channel fragments, phosphoproteins	LC-MS/MS, immunoassays, proximity extension assay	Functional channel status, treatment response
Metabolomic	TCA intermediates, amino acids	NMR, GC/LC-MS	Metabolic dysregulation, mitochondrial function
Extracellular Vesicles	Urinary exosomal miRNAs, lncRNAs (e.g., NEAT1), proteins	Nanoparticle tracking, miRNA-seq, lncRNA-seq, proteomics	Non-invasive monitoring, cell-type specific signals, early pathway activation
Integrated/AI-Driven	Multi-omics feature sets	Deep learning (e.g., Transformer), digital twin simulation	Prognostic/predictive modeling, personalized in silico trials

Abbreviations: NGS, next-generation sequencing; PRS, polygenic risk score; scRNA-seq, single-cell RNA sequencing; cfDNA, cell-free DNA; LC-MS/MS, liquid chromatography-tandem mass spectrometry; NMR, nuclear magnetic resonance; GC/LC-MS, gas/liquid chromatography-mass spectrometry; AI, artificial intelligence.

tension [31-35]. Recent single-cell RNA sequencing (scRNA-seq) studies have unequivocally established immune dysregulation as central to DKD pathogenesis, revealing a dynamic shift in macrophage phenotypes from early pro-inflammatory M1-like to persistent reparative but maladaptive M2-like states [36, 37].

The Mechanical Stress Axis is activated under glomerular hyperfiltration [38]. The mechanosensor PIEZO1 in podocyte membranes translates abnormal tensile forces into calcium influx, upregulating channels like TRPC6 via calcineurin/nuclear factor of activated T-cells (NFAT) pathways, forming a vicious cycle leading to podocyte disruption [39]. Emerging live-imaging data illustrate a spatiotemporal "mechano-electrochemical" coupling model, where PIEZO1-mediated calcium transients activate calcium/calmodulin-dependent protein kinase II (CaMKII), leading to phosphorylation of the ENaC γ-subunit and amplifying sodium reabsorption [40].

The Systemic Metabolite Communication Axis reveals the remote impact of gut microbiota dysbiosis. Alterations in microbial metabolite profiles (e.g., reduced short-chain fatty acids, increased trimethylamine N-oxide (TMAO)) exacerbate systemic and local renal inflammation and oxidative stress, indirectly disrupting renal ion channel network stability [41, 42].

Critically, these pathological axes constitute an ordered molecular program leading to specific "channelopathy phenotypes", such as a "sodium retention phenotype" (ENaC overactivity) or a "podocyte stress phenotype" (TRPC6/PIEZO1-mediated calcium overload) [43]. These specific functional alterations are inevitably accompanied by detectable molecular events, forming the material basis for translating abstract pathogenic mechanisms into clinically applicable, objectively quantifiable biomarkers.

Sources and technological platforms for ion channel-related biomarkers

Ion channel dysfunction can be reflected through changes at multiple levels, from genes to downstream metabolic effects. Modern biotechnologies provide diverse platforms for identifying and quantifying these potential biomarkers (**Table 1**).

Genomic and genetic markers

Individual genetic background influences DKD susceptibility and drug response. Variants in genes encoding ion channels or their regulatory proteins, such as polymorphisms in *SLC5A2* (SGLT2) and *SCNN1* (ENaC subunit), are associated with renal function and blood pressure regulation [44, 45].

Transcriptomic and epigenetic markers

Single-cell RNA sequencing (scRNA-seq) can precisely define expression changes of ion channel genes (e.g., *TRPC6*, *AQP1*) within specific renal cell types (e.g., podocytes, proximal tubular cells), enabling molecular subtyping [46, 47]. Spatial transcriptomics further resolves the localization of these changes, revealing, for example, the co-localization of venous endothelial cells and fibroblasts forming pro-inflammatory niches [36]. Environmentally induced epigenetic modifications, such as DNA methylation, may leave lasting imprints. Urine cell-free DNA (cfDNA) methylation analysis is

a promising non-invasive approach; targeted panels have identified hypermethylation of the *SCNN1G* promoter in urinary cfDNA, which inversely correlates with eGFR decline rate [48, 49].

Proteomic and metabolomic markers

Mass spectrometry (MS) can directly detect shed ion channel protein fragments or their interacting partners in urine [50]. Metabolomics analyzes small-molecule metabolite profiles to reflect functional consequences. Specific metabolic pattern alterations, such as branched-chain amino acid (BCAA) accumulation or tricarboxylic acid (TCA) cycle intermediate disturbances, may be associated with mitochondrial dysfunction triggered by calcium homeostasis imbalance, indirectly indicating ion channel network dysregulation [51, 58].

Extracellular vesicles and non-invasive biomarkers

Extracellular vesicles, particularly exosomes, carry protein, RNA, and lipid information from their parent cells. Urinary exosomes derived from renal cells contain abundant miRNAs, such as the miR-30 family (targeting the SGLT2 pathway) or miR-155 (regulating the SGK1-inflammatory pathway) [59]. Beyond miRNAs, long non-coding RNAs (lncRNAs) in exosomes, such as nuclear enriched abundant transcript 1 (*NEAT1*), have been identified as specific indicators of TRPC6 pathway activation, with elevated urinary levels preceding traditional albuminuria markers [60].

Artificial intelligence and multi-modal integration

The convergence of artificial intelligence (AI) with multi-omics data is revolutionizing biomarker discovery. Deep learning models can integrate diverse data streams - genomic variants, transcriptomic profiles, proteomic fragments, and metabolomic patterns - to identify complex signatures predictive of DKD progression or treatment response [61, 62]. For instance, a transformer-based model incorporating 12 ion channel-related features significantly outperformed conventional clinical models [63, 64]. Furthermore, "digital twin" technology allows for patient-specific in silico modeling to simulate ion channel behavior and predict therapeutic outcomes [65].

Clinical translation and application strategies guided by biomarkers

Integrating ion channel-related biomarkers into clinical practice aims to achieve more refined patient management, treatment optimization, and drug development.

Molecular endotype-based patient stratification

By combining multiple biomarkers (urinary exosomal miRNA profiles, cfDNA methylation signatures), patients can be classified into distinct, therapeutically relevant endotypes.

Endotype A: "Tubular Sodium Retainer". Characterized by biomarkers indicating high SGLT2/ENaC pathway activity (elevated urinary exosomal miR-30 family, hypermethylation of *SCNN1G* [48]). Clinical Action: These patients are predicted to derive maximal benefit from SGLT2 inhibitors and finerenone.

Endotype B: "Podocyte Calcium Stress". Characterized by biomarkers of TRPC6/PIEZO1 pathway activation (elevated urinary exosomal lncRNA *NEAT1* [60], increased urinary PIEZO1 protein fragments). Clinical Action: These patients may be prioritized for clinical trials with novel TRPC6 or PIEZO1 inhibitors [66].

Predicting and dynamically monitoring treatment response

Pre-treatment levels of pathway-specific biomarkers can predict response. For example, real-world evidence suggests that patients with high baseline urinary ENaC activity experience greater cardiorenal benefit from MRA therapy [67]. Furthermore, a swift decline in urinary podocyte-derived exosomal PIEZO1 or *NEAT1* levels after starting a TRPC6 inhibitor could serve as an early pharmacodynamic marker of successful target engagement, weeks before a reduction in proteinuria is observed [68].

Enabling targeted drug development through enriched trial designs

For investigational drugs targeting novel channels like PIEZO1 or TRPC5, biomarker-driven enrichment strategies can dramatically increase the probability of success. A Phase II trial of a TRPC5 inhibitor could use a composite biomarker signature (e.g., high urinary *NEAT1* +

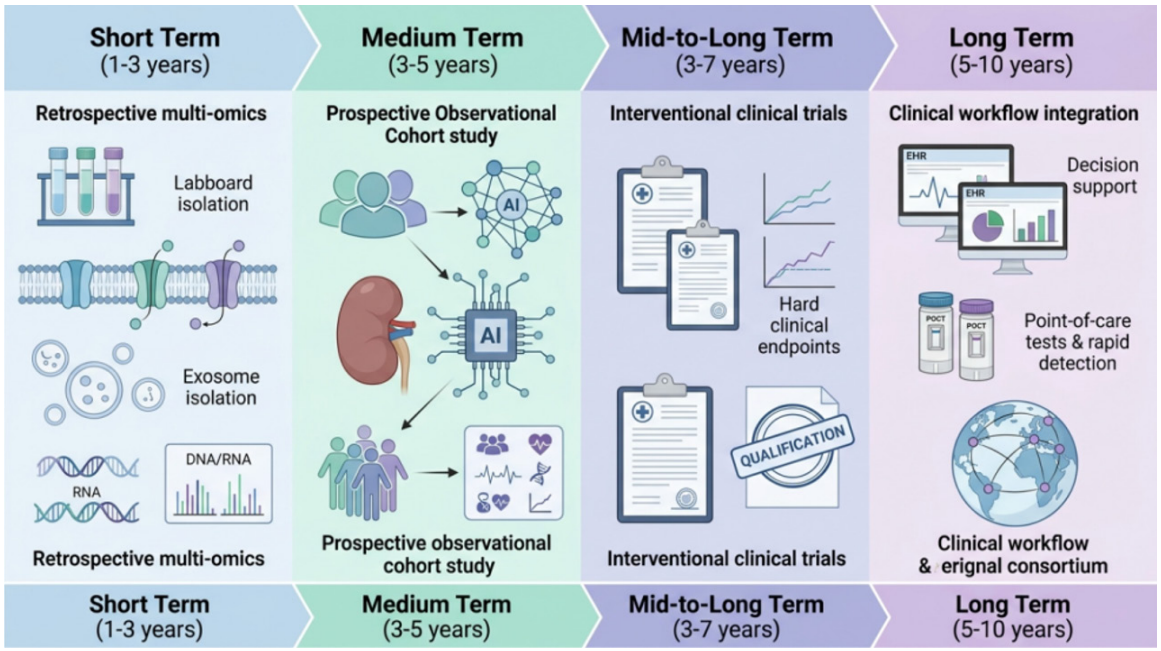

Figure 2. Phased roadmap for biomarker translation in DKD. A timeline illustrating the stages from discovery to clinical integration, highlighting key milestones, study types, and outcomes at each phase.

elevated serum markers of podocyte injury) to select a patient population most likely to respond. This approach has already shown promise, with a recent Phase IIb trial of a TRPC6 inhibitor demonstrating a significant reduction in urinary protein-to-creatinine ratio (UPCR) when combined with an SGLT2 inhibitor [69]. By using these biomarkers as "theranostic" tools, we can de-risk drug development and bring effective targeted therapies to the right patients faster.

Discussion and future perspectives

Viewing ion channels as both pathogenic mediators and biomarker sources represents a significant and clinically actionable expansion of perspective in DKD research. This framework directly complements prior work on ion channel-targeted therapies [12, 70-79] by providing the companion diagnostic strategy necessary for their precision application.

Bridging molecular complexity and clinical utility

The framework transforms disease complexity from a management obstacle into a roadmap for individualized intervention. By systematically capturing the quantifiable molecular outputs of pathogenic pathways (e.g., miRNAs, cfDNA methylation), we can create objective indicators for clinical decision-making, effectively translating deep mechanistic understanding into tools for the clinic [80-87].

A phased roadmap for clinical integration

The translation of ion channel-related biomarkers into routine clinical use is a multi-stage process requiring coordinated efforts (**Figure 2**).

Short Term (1-3 years): Leverage existing biobanks from landmark DKD trials (e.g., CREDENCE, DAPA-CKD) for retrospective multi-omics profiling to identify and validate composite biomarker signatures. Establish assay harmonization standards for key technologies like exosome isolation [51] and cfDNA methylation sequencing.

Medium Term (3-5 years): Establish prospective observational cohorts with multi-modal biomarker sampling that deliberately include under-represented populations. Validate the independent prognostic utility of biomarker panels for hard clinical endpoints (e.g., ≥40% eGFR decline). Develop and validate machine learning-based prediction tools integrating biomarker data with clinical variables [44].

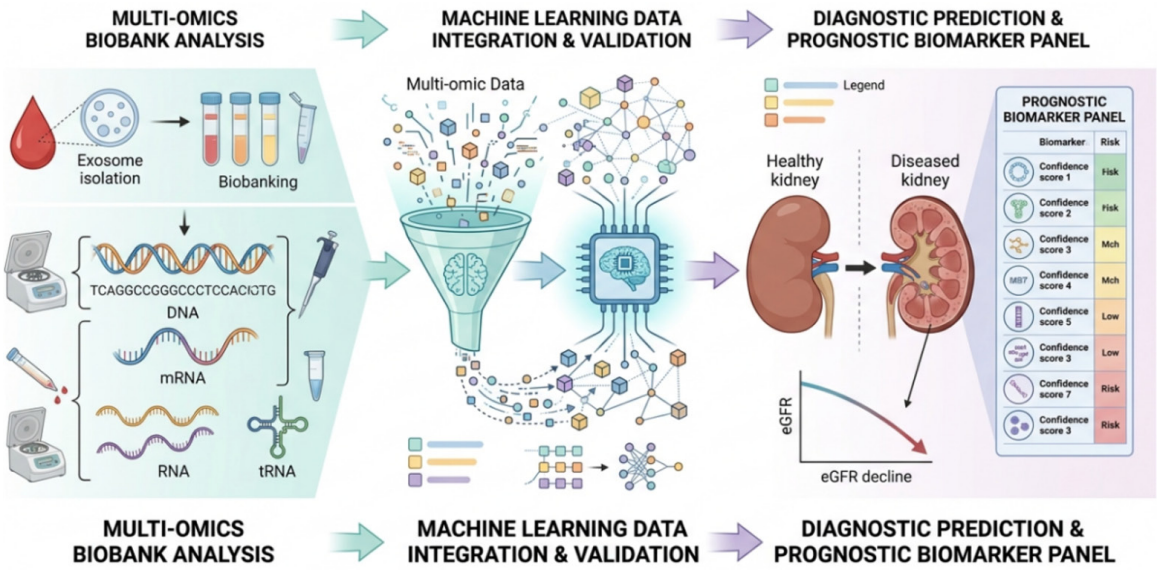

Figure 3. Summary of the dual-role paradigm. The diagram illustrates how pathological axes drive ion channel dysregulation and simultaneously generate quantifiable biomarkers. These biomarkers guide patient stratification, treatment monitoring, and trial enrichment, enabling precision medicine for DKD.

Mid-to-Long Term (3-7 years): Execute prospective, randomized controlled trials testing biomarker-driven therapeutic algorithms, including pragmatic trials comparing biomarker-stratified therapy to standard care and enrichment trials for novel channel-targeted agents (e.g., TRPC5 inhibitors in biomarker-positive subgroups) [88-95]. Engage with regulatory agencies (FDA, EMA) to qualify biomarkers as drug development tools.

Long Term (5-10 years): Achieve regulatory approval for validated multi-analyte assays. Integrate them into clinical workflows via interoperable digital platforms and electronic health record (EHR)-based clinical decision support systems. Develop simplified, cost-effective point-of-care versions for diverse healthcare settings. Establish an "International Ion Channel & Kidney Disease Consortium" to maintain standards, update guidelines, and advocate for equitable access.

Conclusion

The convergence of deep molecular phenotyping and targeted therapy presents a historic opportunity for precision management of DKD [96-105]. By re-examining the dual role of ion channels - as both key pathological effectors and rich sources of biomarkers - we can open a direct translational pathway from disease mechanismstoclinicaldecision-making.Systematically developing and validating ion channel-centric biomarkers is essential for achieving individualized patient stratification, optimizing existing therapies, and efficiently developing new ones. The phased roadmap proposed here provides a structured path forward. Through interdisciplinary and international collaboration, we can construct a dynamic, biomarker-centered precision management system for DKD, finally turning the promise of personalized medicine into a reality for patients (**Figure 3**).

Disclosure of conflict of interest

None.

Address correspondence to: Wenfeng Wang, Department of Cardiology, Wuhan Asia General Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, China. E-mail: m201275943@mail.alumni.hust.edu.cn; Guang Xu, Department of Cardiology, Ezhou Central Hospital, Ezhou, Hubei, China. E-mail: 13607236327@163.com

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