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Reappraisal of Goal-Directed Medical Therapy in Diabetic Kidney Disease: Beyond the Quadruple Therapy Paradigm

Position Paper

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ABSTRACT

Diabetic kidney disease (DKD) affects 40% of individuals with diabetes and is the leading cause of chronic kidney disease worldwide. While the KDIGO guidelines have established quadruple therapy comprising renin-angiotensin system inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and mineralocorticoid receptor antagonists as the cornerstone of DKD management, substantial phenotypic and molecular heterogeneity among patients limits the efficacy of standardized protocols. Emerging evidence highlights distinct DKD subtypes defined by inflammatory, metabolic, fibrotic, and vascular pathobiological pathways, which may warrant tailored therapeutic strategies. Novel biomarkers, including tubular injury markers, inflammatory mediators, and genetic variants such as APOL1, offer opportunities for phenotype-driven treatment. Multi-omic integration, encompassing genomics, transcriptomics, proteomics, and metabolomics, combined with machine learning algorithms, enables the identification of treatment-responsive phenotypes and supports clinical decision-making. Emerging therapeutic targets, including complement system inhibitors, ketone metabolism modulators, and JAK-STAT pathway inhibitors, have further expanded the precision medicine landscape in DKD management. Implementation challenges include biomarker standardization, healthcare infrastructure requirements, cost-effectiveness, regulatory validation, and equitable access to diverse populations. Addressing these barriers through multidisciplinary collaboration, point-of-care diagnostics, and inclusive clinical trials is essential for personalized DKD management. Goal-directed personalized DKD management represents a transformative paradigm with the potential to optimize outcomes, minimize adverse effects, and reduce long-term healthcare costs.

KEYWORDS: Diabetic kidney disease, Precision medicine, Goal-directed therapy, Multi-omics, Biomarkers

The current paradigm and its limitations

Diabetic kidney disease (DKD) affects 40% of individuals with diabetes mellitus and is the leading cause of chronic kidney disease (CKD) globally [1]. Despite evidence-based therapies, DKD progression to end-stage renal disease continues to impose substantial global burdens. The KDIGO 2022 guidelines established quadruple therapy as the cornerstone of DKD management, incorporating renin-angiotensin system inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and mineralocorticoid receptor antagonists [2]. The CREDENCE trial showed that canagliflozin reduced the primary composite outcome of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death by 30% compared to placebo [3]. The DAPA-CKD trial demonstrated that dapagliflozin reduced the primary composite outcome by 39% in patients with CKD [4]. However, post-hoc analyses reveal considerable heterogeneity in treatment responses, challenging standardized protocols. CREDENCE trial subgroup analyses showed patients with higher baseline urinary albumin-to-creatinine ratios (≥300 mg/g) experienced greater renal benefits, while those with preserved estimated glomerular filtration rate showed more cardiovascular protection [3]. This suggests individualized treatment selection may optimize outcomes beyond current algorithms.

Phenotypic heterogeneity in diabetic kidney disease

Recent research has revealed substantial phenotypic diversity in DKD. Traditional classification systems based on albuminuria and estimated glomerular filtration rate fail to capture pathophysiological heterogeneity [5]. Histopathological studies show distinct patterns that may respond differently to specific interventions. Precision medicine has identified multiple DKD subtypes using integrated analyses [6]. These molecular phenotypes correlate with different progression rates and treatment responses, indicating DKD represents distinct pathobiological processes. Genetic studies have identified over 40 susceptibility loci for DKD, including variants affecting glucose metabolism, podocyte function, and inflammatory pathways [7]. APOL1 high-risk genotypes in individuals of African ancestry increase DKD progression risk and may influence treatment selection [8].

Emerging biomarkers for precision medicine

The limitations of traditional markers have prompted investigation of novel markers reflecting specific pathways [9]. Inflammatory biomarkers predict DKD progression independently and may guide anti-inflammatory therapy selection [9]. Tubular injury markers such as kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, and β2-microglobulin provide insights into damage that may precede glomerular dysfunction [10]. These markers could inform early intervention strategies and guide tubular-protective therapies along with precision medicine (Table 1).

Multi-omic integration and clinical decision support

Machine learning algorithms can analyse genomic, transcriptomic, proteomic, and metabolomic data to identify treatment-responsive phenotypes and predict drug responses. The CKD Biomarkers Consortium showed that multi-marker panels outperform single biomarkers in predicting DKD progression [11]. Urinary proteomics and metabolomics provide insights into kidney pathological processes, potentially guiding personalized treatment.

Patient Phenotype	Biomarker Profile	Primary Pathways	Targeted Interventions	Clinical Monitoring
Inflammatory-Dominant	↑TNF-R1, ↑IL-6, ↑CRP	NF-κB activation, inflammasome	Selective anti-inflammatory agents, JAK inhibitors	TNF-R1, IL-6 levels
Metabolic-Driven	↓FGF-21, ↓Adiponectin	mTOR dysregulation, mitochondrial dysfunction	Ketogenic interventions, AMPK activators	FGF-21, metabolic panel
Fibrosis-Prone	↑Galectin-3, ↑ST2	TGF-β signalling, ECM deposition	Anti-fibrotic therapies, pirfenidone analogues	Galectin-3, imaging
Vascular Disease	↑VEGF, ↑Angiopoietin-2	Endothelial dysfunction, angiogenesis	Vascular protective agents, endothelin antagonists	VEGF, vascular studies
Genetic High-Risk	APOL1 variants, family history	Podocyte dysfunction, accelerated progression	Intensive RAS blockade, early SGLT2i	Genetic counselling, frequent monitoring

Table 1. Personalized therapeutic strategies in goal-directed DKD management [5–8]. TNF: Tumour necrosis factor; IL: Interleukin; NF-κB: Nuclear factor kappa beta; CRP: C reactive protein; TGF: Transforming growth factor; Jak: Janus activated kinase; FGF-21: Fibroblast growth factor-21; VEGF: Vascular endothelial growth factor; mTOR: mammalian target of rapamycin; APOL1: Apolipoprotein 1.

Novel therapeutic targets and implementation strategies

Recent insights have identified therapeutic targets beyond those of traditional approaches. Complement system activation is critical in the pathogenesis of DKD, and inhibitors have shown promise [12]. DKD's recognition as a metabolic disorder highlights ketone metabolism as a target, with ketogenic diets potentially providing renoprotective effects through improved mitochondrial function [13]. AGE breakers and JAK-STAT pathway inhibition show promise, particularly in patients with inflammatory phenotypes [5].

Risk stratification and treatment algorithms

The implementation of goal-directed therapy requires risk stratification systems that integrate clinical, genetic, and biomarker data. AI-driven tools can process multidimensional data for personalized treatment. Point-of-care testing can enable real-time therapeutic adjustments. Integration with electronic health records may enhance the physician's ability to implement personalized treatment protocols.

Healthcare system considerations and implementation challenges

Cost-effectiveness and infrastructure requirements transitioning to personalized DKD management requires healthcare system adaptations. Biomarker-guided therapy may reduce long-term costs, despite higher diagnostic expenses. Implementation requires infrastructure investments for biomarker testing, genetic analysis, and data management. Multidisciplinary teams of nephrologists, genetic counsellors, pharmacists and data scientists are essential for DKD management. Telemedicine can provide specialized expertise to underserved regions [14].

Validation and regulatory pathways

The implementation of precision medicine in DKD care faces several challenges. Biomarker standardization, algorithm validation, and therapeutic monitoring protocols require coordinated

research efforts. Clinical trials evaluating biomarker-guided treatments must demonstrate their utility and cost-effectiveness. Advanced trial designs can simultaneously evaluate multiple biomarkers and treatments for regulatory approval.

Equity and access considerations

Without equitable implementation, precision medicine risks increasing healthcare disparities. Access to advanced diagnostics and personalized therapies across socioeconomic groups is challenging. Cost-effective testing and point-of-care diagnostics may help to address these issues. Population-specific biomarker validation is essential, as most research has focused on populations of European ancestry. Including diverse populations in research is crucial for developing inclusive approaches to health.

Future directions and clinical implementation

The future of goal-directed DKD therapy will integrate artificial intelligence, portable diagnostics, and continuous monitoring. Wearable technologies that provide real-time physiological data with biomarker profiles could enable dynamic treatment adjustments. Cloud platforms integrating patient data and treatment algorithms may facilitate collaborative care and specialist consultations, thereby improving outcomes while reducing costs.

The challenge of current research on DKD is to find new and more specific drugs based on the mechanisms of action and multifaceted pathogenesis in DKD. Another significant challenge is understanding which patients' benefit from certain therapeutics rather than others and why certain patients do not respond.

Research priorities should focus on validating precision medicine in diverse populations and developing practical and cost-effective implementation strategies. Large-scale studies comparing biomarker-guided therapy with standard of care are needed. The development of simplified biomarker panels and point-of-care testing is crucial for adoption, while research into optimal treatment algorithms will aid clinical implementation.

Conclusions and future perspectives

The shift toward personalized therapy in DKD management represents a paradigm shift in improving outcomes. Although quadruple therapy has established therapeutic foundations, DKD heterogeneity requires approaches tailored to individual patients. The integration of multi-omic biomarkers, AI algorithms, and novel therapeutic targets offers opportunities for optimizing treatment. However, implementation requires addressing biomarker validation, cost-effectiveness, and clinician education challenges. Moving beyond standardized protocols, precision medicine principles in nephrology may become essential for optimizing DKD management. The benefits include reduced costs, minimized adverse effects, and enhanced patient satisfaction. This transformation will require coordinated efforts from researchers, clinicians, healthcare systems, and regulatory bodies to reimagine DKD management in the precision medicine era.

Data availability statement

The data for substantiating the findings of this study are available with the corresponding author and can be made available on request.

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