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GROWTH DIFFERENTIATION FACTOR-15 IN DIABETIC KIDNEY DISEASE: FROM PATHOPHYSIOLOGICAL MECHANISMS TO CLINICAL APPLICATIONS

FAKTOR DIFERENCIJACIJE RASTA 15 KOD DIJABETESNE BOLESTI BUBREGA: OD PATOFIZIOLOŠKIH MEHANIZAMA DO KLINIČKE PRIMENE

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Summary

Background: Diabetic kidney disease (DKD) remains a major cause of end-stage renal disease worldwide, yet current clinical biomarkers such as albuminuria and estimated glomerular filtration rate lack sufficient sensitivity to detect early renal injury or predict individual disease trajectories. Growth differentiation factor 15 (GDF15), a stress-inducible cytokine belonging to the transforming growth factor-β superfamily, has emerged as a promising molecular link between metabolic stress, inflammation, mitochondrial dysfunction, and renal injury in diabetes. This review systematically synthesizes current experimental and clinical evidence on the role of GDF15 in DKD, with emphasis on its mechanistic involvement in renal pathophysiology and its translational potential as a biomarker and therapeutic target. Evidence from preclinical models and human studies indicates that GDF15 is upregulated in diabetic kidneys, particularly in tubular epithelial cells, in response to hyperglycemia-induced oxidative stress and mitochondrial dysfunction. Mechanistically, GDF15 modulates key pathogenic pathways in DKD, including NF-κB–mediated inflammation, NLRP3 inflammasome activation, macrophage polarization, TGF-β/Smad-driven fibrogenesis, and autophagy regulation through PI3K/Akt and AMPK signaling. Clinically, circulating and urinary GDF15 levels correlate with disease severity and independently predict renal function decline, suggesting utility in both early diagnosis and prognostic stratification. In addition, emerging evidence supports its

Kratak sadržaj

Uvod: Dijabetička bolest bubrega (DBB) ostaje glavni uzrok terminalne bubrežne insuficijencije širom sveta, ali trenutni klinički biomarkeri poput albuminurije i procenjene brzine glomerularne filtracije nemaju dovoljnu osetljivost da bi otkrili rano oštećenje bubrega ili predvideli pojedinačne putanje bolesti. Faktor diferencijacije rasta 15 (GDF15), citokin indukovan stresom koji pripada superfamiliji transformišućeg faktora rasta-β, pojavio se kao obećavajuća molekularna veza između metaboličkog stresa, upale, mitohondrijalne disfunkcije i oštećenja bubrega kod dijabetesa. Ovaj pregled sistematski sintetiše trenutne eksperimentalne i kliničke dokaze o ulozi GDF15 kod DBB, sa naglaskom na njegovo mehanističko učešć e u patofiziologiji bubrega i njegov translacioni potencijal kao biomarkera i terapijske mete. Dokazi iz prekliničkih modela i studija na ljudima ukazuju na to da je GDF15 pojačan u dijabetičkim bubrezima, posebno u tubularnim epitelnim ćelijama, kao odgovor na oksidativni stres i mitohondrijalnu disfunkciju izazvanu hiperglikemijom. Mehanistički, GDF15 modulira ključne patogene puteve kod DBK, uključujući upalu posredovanu NF-κB, aktivaciju inflamazoma NLRP3, polarizaciju makrofaga, fibrogenezu vođenu TGF-β/Smad-om i regulaciju autofagije putem PI3K/Akt i AMPK signalizacije. Klinički, nivoi GDF15 u cirkulaciji i urinu koreliraju sa težinom bolesti i nezavisno predviđaju pad bubrežne funkcije, što ukazuje na korisnost i u ranoj dijagnozi i u prognostičkoj stratifikaciji. Pored toga, novi dokazi podržavaju njegovu potencijalnu

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potential role as a pharmacodynamic marker responsive to interventions such as metformin and SGLT2 inhibitors. However, its context-dependent biological effects, lack of assay standardization, and confounding elevation in systemic diseases remain key challenges. Overall, GDF15 represents a central stress-integrating mediator in DKD pathogenesis and a promising candidate for precision nephrology, warranting further validation in longitudinal multi-omics and interventional studies.

Keywords: growth differentiation factor 15, diabetic kidney disease, renal fibrosis, biomarker, GFRAL signaling, inflammation, oxidative stress, therapeutic target

ulogu kao farmakodinamskog markera koji reaguje na intervencije kao što su metformin i SGLT2 inhibitori.

Ključne reči: faktor diferencijacije rasta 15, dijabetička bolest bubrega, bubrežna fibroza, biomarker, GFRAL signalizacija, upala, oksidativni stres, terapijska meta

Introduction

Background and Significance

Diabetes mellitus has reached pandemic proportions, with the International Diabetes Federation estimating that approximately 537 million adults were living with diabetes in 2021, a figure projected to exceed 780 million by 2045 (1). Among the microvascular complications of this metabolic disorder, diabetic kidney disease affects roughly 30–40% of individuals with type 1 or type 2 diabetes, representing the single most common etiology of end-stage renal disease in developed nations (2). The progressive nature of DKD imposes an enormous socioeconomic burden on healthcare systems worldwide, consuming disproportionate resources for dialysis, transplantation, and cardiovascular comorbidity management.

Contemporary therapeutic strategies centered on intensive glycemic control, renin-angiotensin-aldosterone system blockade, and more recently sodium-glucose cotransporter 2 inhibitors have meaningfully slowed disease progression in many patients (3). Nonetheless, a substantial residual risk persists, and a considerable fraction of individuals continue to experience irreversible nephron loss despite optimized standard of care. This therapeutic gap underscores the pressing need to identify novel molecular mediators that can serve dual roles as early diagnostic biomarkers and actionable therapeutic targets within the complex pathobiology of DKD (4).

Growth differentiation factor 15 has attracted increasing attention in this context. Originally identified as a divergent member of the transforming growth factor-β superfamily, GDF15 is a stress-inducible cytokine whose circulating levels rise markedly under conditions of cellular injury, mitochondrial dysfunction, and metabolic stress (5). In the diabetic milieu, hyperglycemia, advanced glycation end-products, and hemodynamic perturbations converge to upregulate GDF15 expression across multiple renal cell types (6). Emerging evidence positions GDF15 at the intersection of inflammation, oxidative stress, and fibrogenesis—three pathological axes that drive DKD progression—while also linking it to systemic metabolic regulation through its receptor complex GFRAL-RET in the hindbrain (7). The multifaceted involvement of GDF15 in both local renal injury and systemic metabolic signaling provides a compelling rationale for a comprehensive examination of its role in diabetic kidney disease.

Scope and Methodology of the Review

This review adopts a translational framework designed to systematically map the multifaceted roles of GDF15 in diabetic kidney disease, progressing from fundamental biology to clinical application (8). Rather than serving as a descriptive catalog of published findings, the present work constitutes an integrative and critical synthesis that bridges basic science discoveries with translational and clinical perspectives (9). The thematic organization follows a logical trajectory: beginning with GDF15 molecular biology and receptor signaling through the GFRAL-RET complex and downstream effectors including MAPK, PI3K/Akt, and AMPK pathways, then advancing through pathogenic mechanisms encompassing inflammasome activation, macrophage polarization, renal fibrosis, oxidative stress, and autophagy dysregulation, before arriving at clinical biomarker evidence and emerging therapeutic strategies (10).

The integrative nature of this synthesis is central to its methodology. Preclinical mechanistic data derived from animal models and cell-based systems are evaluated alongside clinical cohort evidence examining circulating GDF15 as a diagnostic and prognostic biomarker (11). Multi-omics findings, including transcriptomic, proteomic, and metabolomic datasets, are incorporated to provide a holistic molecular landscape of GDF15 function within the diabetic kidney microenvironment (12). This approach enables identification of convergent pathways where experimental and

clinical observations reinforce one another, while also highlighting discrepancies that demand further investigation.

The scope encompasses original research articles, preclinical studies, and clinical investigations published between 2004 and 2024, capturing the period from early characterization of GDF15 as a stress-responsive cytokine through recent advances in receptor pharmacology and therapeutic analog development (13). By structuring the analysis to culminate in a critical assessment of current limitations and knowledge gaps, this review provides a coherent roadmap for understanding how GDF15 biology may be leveraged within precision nephrology practice.

Literature Search Strategy and Selection Criteria

To ensure a comprehensive and systematic synthesis of the prevailing evidence, a rigorous literature search protocol was executed across primary biomedical databases, specifically encompassing PubMed, Web of Science, and Scopus. The retrieval architecture utilized carefully constructed Boolean logic, integrating key concepts through targeted terms including »GDF15«, »MIC-1«, »NAG-1«, »diabetic kidney disease«, »diabetic nephropathy«, »biomarker«, »fibrosis«, and »signaling«. The temporal framework was strictly delineated to capture articles published between 2004 and 2024, a timeframe corresponding to the accelerated conceptual advancement in characterizing stress-responsive cytokines within metabolic disorders.

Predefined inclusion parameters were established to ascertain the reliability and analytical depth of the synthesized data. The evaluation prioritized original research articles, extensively validated preclinical models, and robustly designed clinical studies. Both English and Chinese language publications were incorporated into the analysis, contingent upon the availability of comprehensive mechanistic elucidations or verifiable clinical outcome datasets. Stringent exclusion criteria were concurrently applied to filter out non-English and non-Chinese literature, isolated case reports, unverified commentary, and studies demonstrating insufficient methodological rigor or lacking granular pathophysiological data. The screening trajectory proceeded systematically through an initial elimination of duplicate records, followed by an independent evaluation of titles and abstracts to isolate relevant investigations. A subsequent exhaustive full-text appraisal was conducted to verify data integrity, experimental reproducibility, and thematic alignment with the core objectives of this analysis.

By meticulously distilling this curated corpus of high-fidelity research, the underlying methodological foundation is secured to support complex biological interpretations. This rigorously validated evidence base seamlessly informs the subsequent granular dissection of molecular pathogeneses, ultimately providing a definitive framework to facilitate the translation of these mechanistic discoveries into precision nephrology diagnostics and rational therapeutic interventions.

Overview of GDF15 Biology and Signaling

GDF15 is a divergent member of the transforming growth factor-β (TGF-β) superfamily, initially identified as macrophage inhibitory cytokine-1 (MIC-1). The protein is synthesized as a 40 kDa precursor containing a signal peptide, a propeptide domain, and a mature domain. Proteolytic cleavage at a conserved RXXR furin-like site releases the mature peptide, which subsequently forms a 25 kDa disulfide-linked homodimer that is secreted into the extracellular space (14). Under basal physiological conditions, GDF15 expression remains relatively low across most tissues, with the placenta representing a notable exception where constitutive high-level expression occurs (15). Cellular stress stimuli, including hyperglycemia, mitochondrial dysfunction, endoplasmic reticulum stress, and reactive oxygen species accumulation, potently upregulate GDF15 transcription through p53-dependent and p53-independent mechanisms.

The canonical receptor mediating circulating GDF15 signal transduction is glial cell-derived neurotrophic factor family receptor alpha-like (abbreviated as GFRAL), a co-receptor that forms a signaling complex with the RET tyrosine kinase (16). GFRAL expression is highly restricted to the area postrema and nucleus tractus solitarius in the hindbrain, where GDF15-GFRAL-RET engagement activates downstream cascades including MAPK/ERK, PI3K/Akt, and PLCγ pathways to regulate energy homeostasis and body weight. Beyond this central axis, GDF15 also modulates AMP-activated protein kinase (AMPK) signaling, influencing cellular energy sensing, lipid oxidation, and mitochondrial biogenesis in peripheral tissues (17).

A growing body of evidence suggests GFRAL-independent signaling mechanisms operating in tissues where GFRAL is not detectably expressed, including the kidney. Proposed alternative interactions involve TGF-β receptor type II (TGF-βRII) and activin receptor-like kinases, though this remains an area of active debate. Such peripheral signaling may mediate local anti-inflammatory and anti-apoptotic effects through Smad-independent and NF-κB-modulatory pathways (18). The dual capacity of GDF15 to

signal through both central GFRAL-dependent and peripheral GFRAL-independent routes underscores its pleiotropic nature and positions it as a molecule whose functional impact in renal pathophysiology extends beyond simple metabolic regulation (19).

Expression Patterns of GDF15 in the Kidney under Diabetic Conditions

The spatiotemporal expression profile of GDF15 within the diabetic kidney provides essential context for understanding its functional relevance in disease progression. Under normal physiological conditions, GDF15 is expressed at relatively low levels in renal tissue; however, the diabetic milieu characterized by sustained hyperglycemia, advanced glycation end-products, and hemodynamic stress dramatically upregulates its expression across multiple renal compartments (20).

Evidence from diabetic animal models has been particularly informative in mapping renal GDF15 expression. In streptozotocin-induced type 1 diabetic mice and db/db type 2 diabetic mice, GDF15 mRNA and protein levels are markedly elevated in the renal cortex and medulla (21). Immunohistochemical analyses reveal that proximal tubular epithelial cells represent the predominant site of GDF15 enrichment under hyperglycemic stress, consistent with the metabolic vulnerability of this cell population to glucose-mediated injury (22). Podocytes and mesangial cells also demonstrate increased GDF15 expression, though to a lesser extent than tubular epithelia. Genetic deletion of GDF15 in these models augmented renal damage in both type 1 and type 2 diabetes, manifesting as exacerbated albuminuria, glomerular hypertrophy, and tubulointerstitial fibrosis, thereby confirming a protective role for locally produced GDF15 in mitigating diabetic renal injury (23).

Transcriptomic profiling from human DKD biopsies corroborates these preclinical observations, demonstrating elevated GDF15 transcript abundance in tubular compartments that correlates with histological severity scores (24). The relationship between intrarenal GDF15 production and systemic circulating levels merits particular attention. While plasma GDF15 concentrations reflect contributions from multiple organs including the liver, heart, and adipose tissue, urinary GDF15 may more specifically indicate kidney-derived synthesis (25). Urinary measurements thus offer a potentially superior indicator of local renal stress compared with plasma levels alone, providing a rationale for employing urinary GDF15 as a compartment-specific biomarker in clinical assessment of DKD severity (26).

GDF15 in Inflammation and Immune Modulation of DKD

Chronic low-grade inflammation constitutes a central pathogenic mechanism in diabetic kidney disease, driven by hyperglycemia-induced accumulation of advanced glycation end-products (AGEs) and sustained activation of innate immune pathways. GDF15 has emerged as a critical modulator within this inflammatory network, exerting context-dependent effects on key signaling cascades including the NLRP3 inflammasome, NF-κB pathway, and macrophage polarization in the renal microenvironment (27).

The AGE/RAGE axis represents a major upstream trigger of renal inflammation in diabetes, activating NF-κB and subsequently upregulating pro-inflammatory cytokines such as TNF-α, IL-6, and MCP-1 (28). A mechanistic study utilizing C57BL/6 mice and HK-2 human proximal tubular cells demonstrated that NAG-1/GDF15 directly inhibits AGE/RAGE-mediated inflammatory signaling in diabetic nephropathy. In this investigation, GDF15 overexpression attenuated NF-κB nuclear translocation and significantly reduced the expression of downstream inflammatory mediators, including TNF-α, IL-6, and MCP-1, both in vivo and in vitro (29, 30). The protective mechanism involved disruption of RAGE-dependent signal transduction, thereby limiting the amplification loop between AGE accumulation and inflammatory gene transcription. These findings position GDF15 as a negative feedback regulator capable of dampening hyperglycemia-driven sterile inflammation within tubular epithelial compartments (31).

Beyond its effects on intrinsic renal cells, GDF15 influences macrophage recruitment and phenotypic polarization within the diabetic kidney. In early-stage injury, elevated local GDF15 expression coincides with increased monocyte infiltration and M1 macrophage activation characterized by production of reactive oxygen species and pro-inflammatory cytokines (32). However, as disease transitions toward chronic adaptation, GDF15 appears to facilitate a shift toward the M2 reparative phenotype, promoting anti-inflammatory cytokine secretion and tissue remodeling (33). This dual capacity reflects the broader understanding that GDF15 functions as a stress-responsive molecule whose net biological effect depends on disease stage, concentration gradients, and local microenvironmental cues. The interplay between GDF15-mediated immune modulation and progressive tissue remodeling extends directly into fibrotic pathways that characterize advanced DKD (34).

GDF15 in Renal Fibrosis and Extracellular Matrix Remodeling

Renal fibrosis, characterized by excessive accumulation of extracellular matrix (ECM) components in both glomerular and tubulointerstitial compartments, represents the final common pathway leading to end-stage renal disease in DKD. GDF15 participates in fibrotic processes through intricate crosstalk with the TGF-β1/Smad signaling axis, connective tissue growth factor (CTGF), and matrix metalloproteinase (MMP) networks, yet its net effect on fibrogenesis remains context-dependent (35).

The TGF-β1/Smad3 pathway is a principal driver of ECM deposition in diabetic nephropathy, and whole transcriptome RNA sequencing has positioned GDF15 as a downstream Smad3-related transcriptome in type-2 diabetic nephropathy (36). This study employed unbiased RNA-seq profiling to identify differentially expressed genes regulated by Smad3 in diabetic kidney tissue, revealing that GDF15 expression is transcriptionally governed by Smad3 binding and contributes to ECM remodeling programs including collagen synthesis and fibronectin assembly (37). These findings establish a direct molecular link between canonical TGF-β signaling and GDF15 induction in the fibrotic diabetic kidney.

Evidence from knockout and overexpression models presents a paradoxical picture. In early-stage DKD, GDF15 upregulation appears to exert protective matrix-remodeling functions by promoting MMP-2 and MMP-9 activity, facilitating degradation of accumulated collagen IV and laminin within the mesangial matrix (38). Conversely, sustained GDF15 elevation in advanced disease stages correlates with enhanced CTGF expression and progressive glomerulosclerosis, suggesting that chronic over-activation overwhelms the homeostatic capacity of GDF15 signaling (39). This biphasic behavior indicates that the balance between profibrotic and antifibrotic actions of GDF15 is critically determined by disease duration and the cumulative burden of metabolic stress. When early adaptive remodeling mechanisms become exhausted, GDF15 may paradoxically reinforce the TGF-β1/Smad3 fibrotic loop, accelerating tubulointerstitial fibrosis progression rather than restraining it (40).

GDF15 in Oxidative Stress, Apoptosis, and Autophagy

Growth differentiation factor 15 functions as a critical stress-responsive mitokine, predominantly released from dysfunctional mitochondria within renal tubular epithelial cells during the metabolic pathogenesis of diabetic kidney disease. The hyperosmotic and hyperglycemic microenvironment exacerbates intracellular reactive oxygen species accumulation, disrupting mitochondrial homeostasis and prompting the rapid upregulation of GDF15 (41). This localized secretion serves as an immediate autocrine and paracrine signal of mitochondrial distress, orchestrating cellular defense mechanisms to mitigate ongoing oxidative damage (42). The capacity of GDF15 to sense and respond to mitochondrial oxidative stress positions it as a vital regulator of cellular integrity in the diabetic kidney.

Upon sensing continuous oxidative injury, GDF15 initiates a profound adaptive autophagy response to counteract programmed cell death. Hyperglycemia heavily induces both podocyte and tubular epithelial apoptosis, driving irreversible structural deterioration (43). GDF15 limits this apoptotic cascade by dynamically modulating intracellular signaling networks, explicitly mediating the intricate crosstalk between the PI3K/Akt/mTOR and MAPK/ERK pathways (44). The suppression of the mTOR complex through PI3K/Akt alterations accelerates autophagosome formation, facilitating the clearance of damaged organelles and toxic protein aggregates (45, 46). The simultaneous activa-tion of the MAPK/ERK cascade enhances cellular resilience and anti-apoptotic gene transcription. This coordinated induction of autophagy fundamentally delays the progression of diabetic tubular injury and preserves renal function under chronic metabolic stress.

The highly oxidative environment of the diabetic kidney is acutely vulnerable to ferroptosis, an iron-dependent form of regulated cell death driven by catastrophic lipid peroxidation (47). GDF15 expression is intricately linked to the pathological regulation of this ferroptotic process. Recent frameworks utilizing ferroptosis-related gene diagnostic models have evaluated the precise severity of diabetic nephropathy, demonstrating that elevated circulating GDF15 levels, alongside other markers, tightly correlate with the progression from early diabetic kidney disease to advanced clinical stages (48). The interplay between GDF15 and lipid peroxidation cascades indicates that GDF15 operates as a compensatory node against iron-driven necrotic degradation (49). The dynamic elevation of GDF15 effectively mirrors the escalating oxidative and ferroptotic burden within the renal microenvironment, acting as both an adaptive survival mechanism and a precise indicator of ongoing tubular cellular fate regulation.

GDF15 as a Novel Early Diagnostic Biomarker for DKD

Early detection of diabetic kidney disease remains challenging because conventional markers such as albuminuria and estimated glomerular

filtration rate (eGFR) often fail to capture incipient tubular and interstitial damage before irreversible structural changes occur (50). GDF15, as a stress-responsive cytokine released from injured renal tubular epithelial cells, offers a promising complementary approach to identifying early-stage DKD, particularly in patients who remain normoalbuminuric despite ongoing renal injury.

Clinical evidence demonstrates a stepwise elevation of serum GDF15 concentrations that parallels DKD severity. In a study stratifying type 2 diabetes patients by urinary albumin excretion rate into normoalbuminuria, microalbuminuria, and macroalbuminuria groups, serum GDF15 levels increased progressively across these stages and correlated positively with cystatin C, complement C1q, and fibroblast growth factor 21, each reflecting distinct dimensions of glomerular and tubulointerstitial dysfunction (51). This graded relationship suggests that GDF15 captures pathological changes that accumulate continuously rather than appearing only after a discrete albuminuria threshold is crossed, thereby providing diagnostic sensitivity in the critical window preceding overt proteinuria (52).

The diagnostic performance of GDF15 is further enhanced when incorporated into multi-marker panels. A study evaluating the combined detection of kidney injury molecule-1 (KIM-1), secreted frizzled-related protein 5 (SFRP-5), and GDF-15 in diabetic nephropathy demonstrated that this triple-biomarker combination yielded higher sensitivity and specificity for early DKD identification than any single marker alone (53). KIM-1 reflects proximal tubular injury, SFRP-5 captures metabolic inflammation and adipokine dysregulation, and GDF15 integrates mitochondrial stress and fibrotic signaling, collectively covering complementary pathogenic axes. Such composite panels address the heterogeneous nature of early diabetic renal injury, where tubular damage, inflammatory activation, and metabolic stress may progress at different rates across individuals (54). The integration of GDF15 into routine clinical assessment panels may therefore improve the identification of patients requiring early therapeutic intervention, particularly among those with preserved albumin excretion who would otherwise escape timely diagnosis.

GDF15 in Predicting DKD Progression and Adverse Renal Outcomes

Beyond its diagnostic value in early-stage detection, GDF15 has attracted considerable attention as a prognostic biomarker capable of predicting the trajectory of renal function deterioration in diabetic populations (55). Prospective cohort studies have consistently demonstrated that elevated circulating GDF15 concentrations are associated with accelerated eGFR decline, progression to end-stage renal disease, and cardiovascular-renal composite endpoints, independent of traditional risk factors such as baseline eGFR, albuminuria, HbA1c, and blood pressure control (56).

A pivotal study investigating urinary GDF15 as a non-invasive prognostic marker enrolled patients with DKD and evaluated whether urinary GDF15 levels could independently predict subsequent renal function decline. The findings revealed that elevated urinary GDF15 concentrations were significantly associated with a faster rate of eGFR loss over the follow-up period, even after adjustment for established clinical predictors including baseline proteinuria and metabolic parameters. This observation suggests that urinary GDF15 reflects intrarenal stress and injury processes that are not fully captured by conventional albuminuria-based staging, thereby offering complementary prognostic information. The non-invasive nature of urinary measurement further enhances its clinical applicability for longitudinal monitoring in outpatient settings.

The incremental prognostic value of GDF15 within multi-biomarker panels has also been systematically evaluated. A recent study assessed the performance of novel biomarkers, including GDF15, for prediction of DKD development and progression in patients with diabetes mellitus. The analysis demonstrated that GDF15, when incorporated alongside other emerging markers, significantly improved risk discrimination compared with models relying solely on traditional clinical variables (13). GDF15 provided additive predictive capacity for identifying patients at highest risk of progressive renal decline, supporting its integration into composite risk stratification algorithms. These findings position GDF15 as an independent risk stratification tool that enhances the precision of prognostic assessment beyond what is achievable with conventional clinical and biochemical parameters alone, warranting validation in larger, multi-ethnic prospective cohorts.

Therapeutic Strategies Targeting GDF15 Signaling in DKD

Current pharmacological and biological interventions modulating GDF15 activity present promising translational potential for mitigating diabetic kidney disease (DKD) progression. Metformin administration consistently induces hepatic and renal GDF15 production, which subsequently triggers downstream metabolic path-ways that alleviate local cellular stress. Experimental application of recombinant GDF15 analogs and specific glial cell line-derived neurotrophic factor family receptor

alpha-like (GFRAL) agonists has demonstrated substantial renoprotective efficacy in preclinical DKD models (57). These agents operate by regulating systemic energy homeo-stasis, suppressing macrophage-driven localized inflammation, and mitigating extracellular matrix deposition. Lifestyle interventions including strict calorie restriction and standardized exercise programs can activate the endogenous GDF15 signaling axis. Such interventions improve systemic metabolic resilience and alleviate hyperfiltration injury of diabetic glomeruli.

Dietary interventions utilizing complex natural compounds provide another viable mechanism to harness the protective properties of the GDF15 pathway. Apple polyphenol supplementation effectively alleviates systemic manifestations of type 1 diabetes and concurrent diabetic nephropathy by upregulating GDF15 expression within renal tissues. This specific dietary intervention attenuates podocyte injury and restores tubular functional integrity through potent antioxidant and anti-inflammatory cascades, establishing how dietary modulators can precisely target the GDF15 axis to limit chronic diabetic tissue damage (58). The preservation of glomerular architecture facilitated by these polyphenolic compounds emphasizes the intrinsic capacity of the GDF15 signaling network to mediate sustained tissue-level defense against chronic metabolic insults.

Moving beyond its utility as a direct interventional target, GDF15 functions as an exceptionally responsive pharmacodynamic biomarker for monitoring treatment efficacy throughout complex DKD clinical trials. Circulating GDF15 concentrations exhibit rapid, dynamic fluctuations in response to modern metabolic pharmacotherapies, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA), and intensive metformin regimens (59). Tracking these quantifiable expression alterations allows investigators to evaluate the molecular responsiveness of the renal microenvironment to hemodynamic off-loading and metabolic correction. The observed shifts in systemic GDF15 levels accurately mirror the progressive resolution of intracellular oxidative stress and fibrotic signaling, providing clinicians with a robust molecular tool to gauge the real-time efficacy of pharmacological strategies aimed at preserving residual glomerular filtration capacity.

Cross-Population and Multi-Omics Evidence Synthesis

The convergence of genetic epidemiology, Mendelian randomization, and high-throughput omics technologies has provided a more granular understanding of how GDF15 contributes to DKD across diverse populations. Genome-wide association studies and candidate gene analyses have identified several polymorphisms within the GDF15 locus that modulate circulating protein levels and may influence renal disease susceptibility. Among these, the rs1058587 (H6D) variant has attracted considerable attention due to its functional relevance in altering GDF15 secretion and its demonstrated associations with chronic kidney disease outcomes (60). A study examining GDF15 gene polymorphisms in end-stage renal disease populations revealed that specific allelic variants were significantly associated with both disease susceptibility and all-cause mortality in CKD patients, suggesting that genetic variation at this locus carries prognostic implications beyond what circulating protein measurement alone can capture. These findings underscore the potential for genotype-informed risk stratification in clinical nephrology, particularly when combined with conventional biomarkers.

Mendelian randomization offers a powerful framework for distinguishing causal relationships from confounding associations (19). Because genetic variants are randomly allocated at conception, they serve as instrumental variables that are less susceptible to reverse causation and environmental confounding. Preliminary Mendelian randomization analyses leveraging GDF15-associated single nucleotide polymorphisms as instruments have begun to address whether elevated GDF15 drives renal decline or merely reflects ongoing tissue injury. Current evidence suggests a bidirectional relationship: kidney damage elevates GDF15 expression through stress-responsive pathways, while genetically predicted higher GDF15 levels may independently influence metabolic and inflammatory processes that accelerate nephropathy. Multi-omics integration—spanning transcriptomics revealing cell-type-specific GDF15 upregulation in tubular epithelial cells, proteomics confirming elevated urinary GDF15 in early DKD, and metabolomics linking GDF15 to altered mitochondrial lipid metabolism—collectively strengthens the biological plausibility of a causal role. Population-specific variations in allele frequencies and effect sizes, however, highlight the need for large-scale, multi-ethnic cohort studies and trans-ancestry meta-analyses to ensure that genetic instruments remain valid across groups (15). Future efforts combining polygenic risk scores with longitudinal multi-omics profiling will be essential for translating these insights into precision medicine strategies for DKD management.

Critical Assessment and Future Directions

Current Limitations and Controversies in GDF15-DKD Research

A central unresolved controversy in the field concerns the paradoxical biological role of GDF15 in diabetic kidney disease. Experimental evidence from acute injury models suggests that GDF15 exerts cytoprotective effects through suppression of inflammatory cascades and attenuation of oxidative damage (44). In contrast, data from chronic disease settings indicate that sustained GDF15 elevation correlates with progressive fibrosis, tubular atrophy, and accelerated loss of renal function. This duality likely reflects differences in experimental models, disease stages, GDF15 concentration ranges, and the duration of cytokine exposure rather than a simple binary classification of the molecule as protective or harmful.

The interpretation of circulating GDF15 levels in clinical cohorts is further complicated by the molecule's responsiveness to multiple systemic stressors beyond diabetic nephropathy. Obesity, heart failure, malignancy, chronic obstructive pulmonary disease, and physiological aging all independently elevate serum GDF15 concentrations (18). In patients with DKD, who frequently present with concomitant cardiovascular comorbidities and metabolic syndrome, attributing GDF15 elevations specifically to renal pathology remains problematic. Disease-specific diagnostic cutoff values have not been validated across diverse populations, and the additive or synergistic contributions of coexisting conditions to GDF15 levels remain poorly characterized.

Methodological heterogeneity also limits cross-study comparisons. No internationally standardized assay platform exists for GDF15 quantification, and commercially available immunoassays differ in antibody specificity, calibration standards, and analytical sensitivity. This variability introduces measurement bias that complicates meta-analytic synthesis and hampers the establishment of universal reference ranges applicable to nephrology practice.

At the mechanistic level, while signaling through the GFRAL-RET receptor complex in hindbrain neurons is well characterized, the pathways mediating GDF15 actions in renal parenchymal cells remain incompletely defined. GFRAL expression in kidney tissue is negligible or absent, implying that GDF15 engages alternative, yet unidentified receptors or co-receptors to modulate tubular epithelial cell behavior, podocyte survival, and mesangial cell activation (28). Until these GFRAL-independent signaling mechanisms are elucidated, therapeutic strategies targeting the GDF15 axis in DKD will lack the molecular precision required for rational drug design.

Future Research Directions and Methodological Recommendations

Addressing the gaps identified in current GDF15-DKD research requires a coordinated, multi-pronged investigative strategy that spans from molecular dissection to clinical validation. The development of kidney-specific conditional GDF15 overexpression and knockout models represents a critical priority, as existing whole-body knockout approaches cannot distinguish renal autocrine/paracrine contributions from systemic endocrine effects (39). Cre-lox systems driven by nephron segment-specific promoters—such as nephrin for podocytes, Ksp-cadherin for tubular epithelium, or P0 for interstitial fibroblasts—would enable precise attribution of GDF15 functions to individual cell populations within the diabetic kidney microenvironment.

Single-cell and spatial transcriptomic technologies offer unprecedented resolution to map the cellular sources and targets of GDF15 across DKD progression. Integrating single-nucleus RNA sequencing with spatial platforms such as MERFISH or Visium would reveal whether GDF15 expression shifts from proximal tubular cells to inflammatory infiltrates or myofibroblasts as disease advances, providing mechanistic insight into its dual protective and injurious roles (41).

Longitudinal multi-center cohorts incorporating serial GDF15 measurements at defined intervals are essential to determine whether trajectory patterns—rather than single time-point values—carry superior prognostic information for eGFR decline and progression to end-stage renal disease. Such studies should enroll ethnically diverse populations and collect concurrent multi-omics data, including proteomics, metabolomics, and epigenomics, to position GDF15 within broader molecular networks.

The establishment of standardized, internationally validated GDF15 immunoassays with harmonized calibrators and defined reference ranges stratified by age, sex, and comorbidity status remains an unmet need (19). Clinically meaningful cutoff values for DKD staging and prognostication must be derived through rigorous receiver operating characteristic analyses across independent validation cohorts, ensuring reproducibility across laboratory platforms.

Well-designed interventional trials—whether testing metformin-mediated GDF15 induction, recombinant GDF15 analogs, or GFRAL-targeted modulators—should incorporate pharmacodynamic endpoints linking drug exposure to GDF15 pathway activation and downstream renal outcomes, thereby bridging the persistent gap between preclinical promise and therapeutic application in human DKD (31).

Implications for Clinical Translation and Discipline Advancement

The trajectory of GDF15 research in diabetic kidney disease illustrates a broader paradigm in which stress-responsive cytokines serve as molecular integrators of metabolic, inflammatory, and fibrotic injury pathways. Rather than reflecting a single pathogenic axis, circulating GDF15 levels encode information about mitochondrial dysfunction, inflammasome activation, macrophage polarization, and extracellular matrix remodeling simultaneously. This multidimensional signaling profile positions GDF15 as a unifying biomarker framework for understanding the convergence of heterogeneous injury mechanisms that characterize progressive nephropathy in diabetes (5).

From a translational standpoint, the integration of GDF15 into risk prediction algorithms holds considerable promise for precision nephrology. Current clinical models rely heavily on albuminuria and estimated glomerular filtration rate, both of which lack sensitivity for early-stage disease and fail to capture the metabolic stress burden that precedes overt structural damage. GDF15, with its demonstrated capacity to detect subclinical renal injury prior to albuminuria onset and to independently predict eGFR decline, offers a complementary dimension to existing risk stratification tools. Incorporating GDF15 into composite panels alongside conventional markers may refine patient phenotyping and enable earlier therapeutic intervention (27).

Equally significant is the potential role of GDF15 as a companion diagnostic and pharmacodynamic surrogate endpoint in clinical trials of novel renoprotective agents. Patient enrichment strategies guided by baseline GDF15 levels could identify individuals at highest risk for rapid progression, thereby increasing statistical power and reducing trial duration. Recent evidence supports this approach: serum GDF15 combined with Nrf2 levels demonstrated predictive value for prognosis assessment in patients with type 2 diabetic kidney disease, suggesting that these markers can stratify therapeutic responsiveness and monitor treatment efficacy in real time (60). Such applications would accelerate the evaluation of candidate therapies, including metformin-mediated GDF15 induction and recombinant analogs currently under preclinical investigation.

Looking ahead, the realization of these translational goals requires validation across diverse populations, standardization of GDF15 assay platforms, and prospective interventional trials designed to test whether GDF15-guided treatment decisions improve hard renal endpoints. Multi-omics integration linking GDF15 dynamics to transcriptomic, proteomic, and metabolomic signatures will further clarify the cell-type-specific contexts in which GDF15 transitions from adaptive protection to maladaptive injury propagation, ultimately informing targeted therapeutic modulation within the expanding toolkit of precision nephrology.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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