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Diagnostic and Prognostic Significance of miRNA-21 and miRNA-146a in Patients with Type 2 Diabetes Mellitus and Nephropathy.

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KEYWORDS

Type 2 diabetes mellitus; Diabetic nephropathy; miRNA-21; miRNA-146a; MicroRNAs; Biomarkers; Renal fibrosis; Inflammation.

ABSTRACT:

Type 2 diabetes mellitus (T2DM) is the most common cause of chronic kidney disease, with complications of diabetes nephropathy. Several microRNAs are associated with an inflammatory and fibrotic mechanism implicated in the cellular pathways of diabetic kidney injury, including miRNA-21 and miRNA-146a. To enquire about the potential diagnostic and/or prognostic value of miRNA-21 and miRNA-146a among type 2 diabetes mellitus patients with or at risk for diabetic nephropathy. Methods. This systematic review followed PRISMA guidelines. Four electronic databases (PubMed, Scopus, Web of Science, and the Cochrane Library) were searched from January 2014 to December 2025. Studies measuring the expression and clinical value of miRNA-21 and miRNA-146a in T2DM and diabetic nephropathy were sought. miRNA-21 and miRNA-146a may represent candidates for further exploration in terms of their diagnostic and prognostic utility in type 2 diabetes mellitus patients and diabetic nephropathy. Their use in clinical settings could aid in early recognition, refine risk stratification, and potentially support tailored approaches to management and disease prevention.

1. Introduction

Diabetic kidney disease (DKD) is the most important worldwide cause of end-stage kidney disease and also significantly contributes to cardiovascular morbidity and mortality in patients with diabetes mellitus. Despite modern use of common biomarkers like albuminuria and estimated glomerular filtration rate, we remain limited in early diagnosis and prognostication, as these biomarkers typically reflect moderate to severe renal damage which is often only partially reversible. In this context, circulating microRNAs provide one class of possible non-invasive biomarkers that could provide snapshot information about underlying inflammatory, fibrotic, and metabolic processes relevant in DKD [1].

2. Diabetic Kidney Disease: Pathophysiology and Diagnostic Challenges

Epidemiology and Clinical Burden

Diabetic kidney disease (DKD) affects 20-40% of people with type 2 diabetes mellitus and is one of the most common and clinically relevant complications of diabetes. Worldwide, DKD accounts for 30–50% of end-stage renal disease (ESRD)[1] which places a large demand on health systems for patients requiring dialysis or kidney transplantation. In addition to renal outcomes, DKD is associated with increased cardiovascular mortality (about 10-20 times higher among individuals with diabetes who have dyspnoea compared to those without nephropathy)[1]. Regarding economic impact, DKD represents the majority of diabetes-related healthcare costs. The hospitalization, prolonged treatment and complications of DKD represent a burden on our health system. [2]

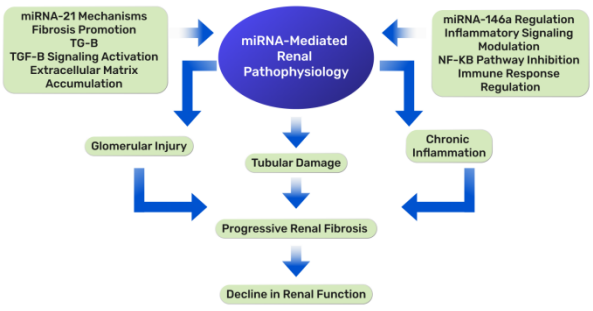

Figure 1. Molecular Role of miRNA-21 and miRNA-146a in the Pathogenesis of Diabetic Nephropathy.

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Schematic representation illustrating the regulatory role of miRNA-21 and miRNA-146a in the pathogenesis of diabetic nephropathy in type 2 diabetic patients, centred respectively on the susceptible node "miRNA-Mediated Renal Pathophysiology" (shaded in deep blue) branching to generate two signalling networks, miRNA-21 modules (fibrosis promoting, TGF-β signalling activation, ECM accumulation) and miRNA-146a signalling modulation (inflammatory signalling, NF-κB inhibition, immune response regulation). Arrowheads link pathogenic facets of glomerular injury, tubular damage, chronic inflammation, and progressive renal fibrosis to the instances of decline in the renal function [3].

Pathophysiology of Diabetic Kidney Disease

Diabetic kidney disease (DKD) is a heterogeneous syndrome that involves hemodynamic, metabolic, inflammatory, fibrotic, and oxidative processes. Hemodynamic alterations including glomerular hyperfiltration and intraglomerular hypertension denote early changes in glomerular filtration barrier leading to increase in mechanical stress. Chronic hyperglycemia fuels metabolic dysregulation by promoting advanced glycation end-product formation, polyol pathway activation, and protein kinase C signaling, which subsequently impact cellular function and structure. Inflammation plays a central role as leukocyte infiltration (especially of macrophages) and increased expression of IL-1β, TNF-α, IL-6 amplify tissue injury. The fibrotic remodeling especially involves transforming growth factor-β drives the accumulation of extracellular matrixes lead to loss of podocytes and glomerulosclerosis, respectively. In addition to this, mitochondrial dysfunction and production of reactive oxygen species further amplify cellular injury. [4]

Clinical Staging and Progression

DKD progression is generally divided into stages from early hyperfiltration to end-stage renal disease, marked by increased glomerular filtration rates, development of microalbuminuria then macroalbuminuria, indicating significant glomerular damage.

As the disease progresses and the eGFR continues to decline, severe renal impairment leads to renal failure. Urinary albumin-to-creatinine ratio, eGFR and serum creatinine are still the hallmarks of diagnosis and monitoring but have major limitations in that there are high biological variability of albuminuria and its absence in a significant number of progressive disease cases, and a decline in eGFR typically occurs only when significant nephron loss has already happened. [5]

Unmet Need for Novel Biomarkers

A key unmet need in DKD is a biomarker for early disease identification, risk stratification, and treatment response. It is estimated that 30–40% of patients develop normoalbuminuric DKD with declining renal function despite normal albumin excretion, which is a clear failure of the albuminuria-based concept of diagnosis. Currently available biomarkers are unable to identify rapid progressors, Pickering et al. have demonstrated the value of circulating microRNAs as potential outstanding molecular biomarkers of DKD. Both of these may indicate ongoing pathology, long before structural damage occurs in the kidneys. [6]

2. **MicroRNAs: Biology and Role in Diabetic Kidney Disease**

MicroRNA Biogenesis and Function

MicroRNAs (miRNAs) are small (~18-25 nt) single-stranded non-coding RNA molecules. They are typically derived from long hairpin transcripts that are transcribed by RNA polymerase II to yield primary miRNA. They are subsequently processed by the enzymes Drosha and DGCR8 to yield precursor miRNA, which are exported from the nucleus via Exportin-5 to the cytoplasm, further cleaved by Dicer into small RNA duplexes and incorporated into the RNA-induced silencing complex (RISC). They bind rmRNA to facilitate degradation of the mRNA transcripts or the inhibition of translation. [7]

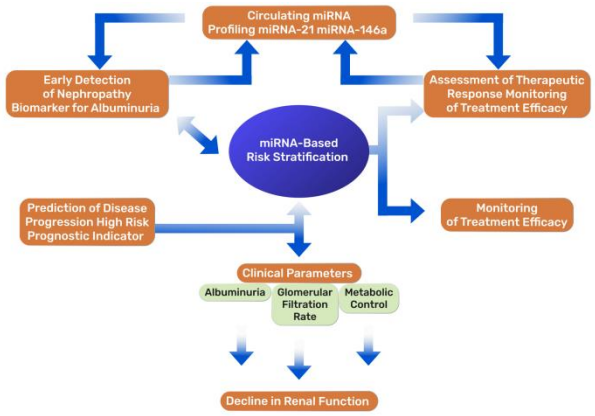

Figure 2. Diagnostic and Prognostic Utility of miRNA-21 and miRNA-146a in Diabetic Nephropathy.

Overview illustrating the applications of circulating miRNA-21 and miRNA-146a as biomarkers in T2D patients, all relating to "miRNA-Based Risk Stratification" (all colored dark blue); Boughs branched from circulating miRNA profiling (the serum and urinary levels of miRNA-21 and miRNA-146a) to diagnosis and

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prognosis (early diagnosis of nephropathy, prediction of disease progression, and assessing the pregnancy women response to treatment). Side modules on how this is done in conjunction with albuminuria, glomerular filtration rate, and metabolic control MOdynamics. Arrows depicting how miRNA-based biomarker assessment can facilitate timely diagnosis, monitor deterioration or improvement of disease, and use personalisation in the management of diabetic nephropathy. [8]

Circulating miRNAs as Biomarkers

Circulating miRNAs are freely circulating miRNAs released to the biological fluids through exosomal secretion, microvesicle secretion or release from apoptotic bodies or bound to an RNA-binding protein such as Argonaute. These processes protect the miRNAs from degradation and are responsible for their noted stability in plasma, serum and urine. Their stability and the fact that they can be detected by qPCR and NGS makes them attractive candidates for non-invasive biomarkers. Certain miRNAs also have tissue specific expression patterns and can provide information on organ specific pathology. In DKD, circulating miRNAs dynamically change with hyperglycemia, inflammation and fibrosis and provide information on disease activity and outcomes[9].

miRNA-21: Structure, Targets, and Functions

miRNA-21 is another extensively studied microRNA in diabetic kidney disease, that is consistently associated with profibrotic and pro-inflammatory signalling. On chromosome 17q23.2 that is evolutionarily conserved, miR-21 targets multiple genes regulating cell survival, apoptosis, and extracellular matrix. Downregulating PTEN, miR-21 activates PI3K/AKT pathway to promote cell survival and proliferation. PDCD4, when suppressed, reduces apoptosis, and inhibition of TIMP3 modulates extracellular matrix metalloproteinase (MMP) activity enhancing degradation of ECM contributing to fibrosis. miR-21 potentiates transforming growth factor-β (TGF-β) signalling, further driving epithelial-to-mesenchymal transition, and myofibroblast activation. Using a db/db mouse model of DKD, miR-21 is upregulated in both glomerular and tubular compartments, which plays a role in podocyte injury, tubulointerstitial fibrosis and recruitment of inflammatory cells, making such a pathogenic key mediator a possible therapeutic target. [10]

miRNA-146a: Structure, Targets, and Functions

Unlike miR-21, miRNA-146a assumes an anti-inflammatory and protective antivirus role in DKD. Encoded on chromosome 5q33.3, miR-146a targets TRAF6 and IRAK1, critical members of the inflammatory signaling cascade, dampening the ensuing NF-κB activation. Functioning as a 27329285 response regulator that regulates the inflammatory response, miR-146a influences macrophage polarization toward the anti-inflammatory M2 phenotype, and modulates oxidative stress signalling. In the diabetic vitiated environment, downregulation of miR-146a in hyperglycemia robs it of it repressive effect, enhancing inflammatory signalling. Decreased levels of miR-146a have been tied to increase oxidative stress, sustained inflammation and rapid progression of DKD. [11]

miR-21 vs. miR-146a: Yin and Yang in Diabetic Nephropathy

The relationship between miR-21 and miR-146a is a prime example of negative regulation in diabetic kidney disease. While miR-21 gains the upper hand and participates in fibrosis, inflammation and tissue remodeling, miR-146a tries to halt the inflammatory signalling and oxidative stress and restores homeostasis. In DKD all these activities are dysregulated with upregulation of miR-21 and downregulation of miR-146a tilting the balance towards pro-inflammatory and pro-fibrotic. Such a state leads to damage and dysfunction of the organ at an accelerated speed. The ratio between the two has therefore been proposed as a composite biomarker of the state of the disease, recognizing both the inciting and protective (compensatory) mechanisms. The clinical utility of such a ratio may far be better than the use or simply using the two separate biomarkers, in a similar fashion as other biomarkers in composite models in precision nephrology. [12]

4. **Circulating miRNA-21 in Diabetic Kidney Disease**

Diagnostic Performance of Circulating miR-21

Systematic Review and Meta-Analysis Evidence

Circulating miR-21 has emerged as one of the most validated and reproducible microRNA biomarkers for diabetic kidney disease diagnosis, accumulating meta-analytic evidence. A pooled analysis by Li et al. of 18 studies (total patients 2847) found that miR-21 had a sensitivity of 78% and specificity of 82%, with an AUC of 0.86, solid discriminative capacity. miR-21 has diagnostic performance exceeding that of traditional albuminuria (AUC 0.79 in same analysis), and is therefore well capable of diagnosing subclinical disease. [13]

Studies Demonstrating Elevated miR-21 in DKD

There are multiple independent studies demonstrating the increased levels of circulating miR-21 in patients with DKD as compared to diabetic patients with no nephropathy. Zhao et al. (2021) showed that serum miR-

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21 was increased 2.8-fold in DKD patients; Wang et al. (2022) observed a positive correlation between urinary miR-21 and albuminuria and an AUC of 0.81 for disease detection; and Koga et al. (2023) found a stage-dependent increase of plasma miR-21 that was highest in macroalbuminuric patients at 3.5-fold higher than controls. To add validation, Al-Kafaji et al. (2024) demonstrated that a miR-21 AUC of 0.89 could be achieved as a biomarker independent of confounding clinical variables. Taken together, studies demonstrate that miR-21 is a sensitive and reproducible biomarker of renal injury and progression of disease. [14]

Correlation with Disease Severity

Beyond the potential diagnostic power of miR-21, levels of circulating miR-21 seems to correlate strongly with markers of disease severity known to be biologically relevant. Levels of miR-21 in circulation are positively correlated with urinary albumin-to-creatinine ratio (UACR), correlation coefficients in a meta-analysis ranged from 0.55 to 0.70 suggesting association with increased glomerular damage. Conversely miR21 is inversely correlated with eGFR suggesting declining renal function. Levels of circulating miR-21 increase across stages of diabetic kidney disease (DKD) from modest levels in normoalbuminuric patients, to marked upregulation in macroalbuminuric disease, miR-21 levels appeared to correlate with biomarkers of tubular injury such as KIM-1 and NGAL. Suggesting that miR-21 may capture both glomerular and tubulointerstitial injury, serving as a measure of overall renal injury [15].

Prognostic Significance of Circulating miR-21

Prediction of DKD Progression

Longitudinal cohort studies show that miR-21 levels at baseline are strong predictors of progression. In a three-year follow-up of 320 patients with type 2 diabetes, Liu et al (2023) found that those with levels of miR-21 exceeding a twofold increase had a 3.2-fold higher risk for DKD progression, while Zhang et al (2024) reported a more rapid decline of renal function in patients in the highest quartile of miR-21 compared to those in lower quartiles (−4.2 mL/min vs −1.8 mL/min eGFR annually). miR-21 adds incrementally to traditional markers at baseline conferring additional predictive ability leading to improvement in its AUC.[16]

Association with Renal and Cardiovascular Outcomes

Elevated circulating miR-21 is also associated with adverse clinical outcomes beyond kidney disease progression that include cardiovascular morbidity and mortality. Kidney disease patients with high baseline miR-21 had a greater than fourfold increased risk of progression to end-stage renal disease. miR-21 also independently predicts major adverse cardiovascular events (hazard ratios approaching 1.8) and is also associated with twofold increased all-cause mortality. These findings illustrate the systemic consequences of elevated miR-21 and indicates a role as a biomarker of global disease burden in DKD. [17]

Dynamic Changes and Treatment Response

Elevated circulating miR-21 is also a marker of adverse clinical outcomes apart from kidney disease progression, including cardiovascular morbidity and mortality. Kidney disease patients with high baseline miR-21 had over a fourfold greater risk of ending up progressing to end-stage renal disease, and miR-21 independently predicts major adverse cardiovascular events (hazard ratios nearing 1.8), and is associated with double the all-cause mortality as well. [17]

Mechanistic Insights from Clinical Studies

Clinical studies have moreover provided mechanistic evidence for miR-21 to be a critical effector of DKD. Circulating miR-21 was positively correlated with TGF-β1 and PAI-1 and collagen IV, fibrogenic factors associated with renal tubulointerstitial fibrogenesis. Higher circulating miR-21 levels was also associated with inflammation (IL-6, TNF-α, CRP) and oxidative stress (8-OHdG, malondialdehyde), while being negatively correlated to total antioxidant capacity. Higher miR-21 score was associated with lower PTEN expression and higher functionality of AKT. Together, these results shed light into the associations of miR-21 with inflammation, fibrosis and cell survival in DKD. [19]

5. **Circulating miRNA-146a in Diabetic Kidney Disease**

Diagnostic Performance of Circulating miR-146a

Systematic Review and Meta-Analysis Evidence

A circulating microRNA that might act as a complementary biomarker to miR-21 is a pro-inflammatory miR-146a. A meta-analysis of 15 studies with 2,103 participants calculated the sensitivity of this biomarker at 74% and specificity at 79%, with a corresponding AUC of 0.81. While the performance seems slightly inferior to miR-21, the true value lies in combining miRNA markers to improve the performance, giving miR-146a an AUC of 0.92 when paired with miR-21 ci miR-146a is also an important biomarker that adds value to a multi marker approach.[20]

Studies Demonstrating Reduced miR-146a in DKD

In contrast to miR-21, circulating miR-146a is consistently downregulated in DKD patients. Al-Kafaji et al. found a 60% decrease in serum miR-146a levels in

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DKD patients compared to diabetic controls and Eissa et al. demonstrated a strong inverse correlation between urinary miR-146a and albuminuria. Increases in miR-146a were progressive with advances in disease stage and lower in macroalbuminuric where patients experienced more inflammation. The independent diagnostic value was confirmed by Lee et al., with an AUC of 0.84 post multivariate adjustment, endorsing the role of miR-146a as a marker of impaired anti-inflammatory regulation in DKD.[21]

Correlation with Disease Severity

Lower levels of circulating miR-146a represent key features of disease severity as they correlate with albuminuria levels and markers like eGFR; lower levels accompany greater excretion of albumin and failure of renal function is reflected by lowered eGFR. miR-146a level progressively declines across stages of DKD suggesting the progressive nature of declining miR-146a levels - which further demonstrates its status as an inflammation modulator in correlating with inflammatory markers itself such as IL-6, TNF-α and hs-CRP. [22]

Prognostic Significance of Circulating miR-146a
Prediction of DKD Progression

Longitudinal studies reveal that reduced miR-146a levels are predictive of adverse renal outcomes. Chen et al. (2023) found that patients with baseline miR-146a levels less than 0.5-fold exhibited 2.8-fold greater risk for disease progression over 3 years, while Kim et al. (2024) showed that low miR-146a levels correlated with declined rates in renal function. [23]

Association with Renal and Cardiovascular Outcomes

Low circulating miR-146a is correlated with higher risk of development of end-stage renal disease, cardiovascular events and mortality. Patients with low levels of miR-146a suffered a three-fold risk of ESRD and double risk of cardiovascular events and death suggesting that this messenger located in circulating molecules of blood is used as a biomarker of systemic inflammatory dysregulation and disease severity. [24]

Dynamic Changes and Treatment Response

Similar to miR-21, miR-146a is also dynamically responsive to therapies, with elevations in miR-146a seen in ACEi/ARB-treated patients, especially in responders. miR-146a upregulation has also been noted in patients treated with SGLT2i and GLP-1 receptor agonists (empagliflozin, liraglutide), associated with renal parameter improvement, supporting its utility as a pharmacodynamic biomarker reflecting restoration of anti-inflammatory pathways [25].

Mechanistic Insights from Clinical Studies

Mechanistically, reduced miR-146a is associated with enhanced activation of the NF-κB pathway and increased expression of its target genes TRAF6 and IRAK1. Conversely, miR-146a correlates with anti-inflammatory cytokines such as IL-10 and negatively with oxidative stress markers. These findings underscore its crucial role as a regulator of inflammatory and oxidative pathways in DKD. [26]

6. **Combined miRNA-21 and miRNA-146a Panels**
Rationale for Combined Panel

The pairing of miR-21 with miR-146a gives a biologically sensible and clinically powerful biomarker panel, incorporating not just the pro-inflammatory/profibrotic pathway but also the anti-inflammatory component. The ratio of miR-21:miR-146a indicates the downweighting of the protective aspect of the pathway by injury-promoting factors, embodying a more comprehensive picture of disease activity. [27]

Diagnostic Performance of Combined Panels

Combined panels are even better than individual biomarkers; meta-analysis shows sensitivity of 86%, specificity of 88% and AUC 0.92. The miR-21/miR-146a ratio makes clinical interpretation even easier: study defined cutoffs give good diagnostic accuracy and separate out disease severity well. [28]

Prognostic Performance of Combined Panels

This combined biomarker signature is highly prognostic for rapid progression, ESRD and mortality with high miR-21 and low miR-146a levels defining a high-risk cohort. Higher ratio scores accurately predict outcomes, acute decline in renal function, and prognosis. [29]

Integration with Traditional Biomarkers

The incorporation of miRNA panels with standard markers such as albuminuria and eGFR into combined models yields significant gains in diagnostic and prognostic capacity (up to AUC 0.96) consistent with precision medicine. [30]

7. Urinary miRNAs: Proximal Biomarkers of Renal Injury
Urinary miRNA-21 in DKD

Urinary microRNAs are even more exciting because they are just so ‘close to home’. These are more informative biomarkers, derived as they are from the site of injury.

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Amongst them is miRNA-21, associated with glomerular and tubulointerstitial damage. One major advantage of urinary miR-21 is the ease of collection - urine is stable at room temperature for 48 hours and is not destroyed following several freeze-thaw cycles. As such and all together, this may lend itself to routine clinical diagnostics and screening programmes. [31] As for the cellular source of urinary miR-21, the miRNA is derived from exosomes released from tubular epithelial cells, podocytes and glomerular endothelial cells. The cellular source ensures that urinary miR-21 reflects on-going pathological processes in the kidney rather than changes taking place elsewhere in the body. Urinary miR-21 achieves area under curve between 0.81 and 0.85 for DKD in diagnostic studies. This is high discriminative capacity. Urinary miR-21 also correlates favourably with albuminuria (correlation coefficients 0.58-0.70), indicating an association with increased glomerular permeability and damage. [32] Urinary miR-21 also correlates with traditional tubular injury markers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). These correlations imply that miR21 picks up early tubulointerstitial damage which might otherwise not be recorded. Relative to circulating miRNAs, urinary miR-21 is less affected by systemic inflammation, giving it a specificity for kidney disease, indicating earlieror "subclinical" localized renal injury. [33]

Urinary miRNA-146a in DKD

Urinary miR-146a, unlike miR-21, acts as an anti-inflammatory biomarker, indicating loss of protective regulatory control in diabetic kidney disease. Diagnostic performance studies show that urinary miR-146a has an AUC from 0.78 to 0.82, indicating clinically relevant accuracy for DKD diagnostics. [34]

Urinary miR-146a levels are inversely related to albuminuria, correlation coefficients of −0.55 to −0.68 imply that lower levels indicate greater glomerular damage. Similar to this relationship, reduced urinary miR-146a results in higher markers of tubular injury. [35]

Prognostically, low urinary miR-146a is associated with more rapid decline in renal function defined by eGFR, supporting its utility in identifying at risk patients. Mechanistically, the reduced miR-146a indicates less inhibition of inflammation in particular NF-κB signalling, leading to chronic inflammation and fibrosis in the kidney. [36]

Exosomal miRNAs

Urinary exosomes, a pre-packaged source of renal biomarkers, are secreted by all major renal cell types (podocytes, tubular epithelial cells, endothelial cells etc.[37]). Exosomal miR-21 is elevated in patients with DKD and has greater diagnostic accuracy than total urinary miRNA (AUC ~0.89), highlighting the selective packaging of some miRNAs into exosomes; this may contribute to diagnostic accuracy via protection from degradation and enrichment of disease signals[38]. In contrast, urinary exosomal miR-146a is reduced in DKD (AUC ~0.85), reflecting defective anti-inflammatory signaling circuit within the kidney. The ratio of exosomal miR-21/miR-146a exhibits remarkable diagnostic performance (AUC 0.94), being possibly the most promising biomarker composite for DKD, incorporating features of a pathogenic (miR-21) and protective (miR-146a) passport[39].

Urinary vs. Circulating miRNAs: Comparative Performance

Both urinary miRNAs and circulating miRNAs are complementary in their value in diabetic kidney disease assessment. Circulating miRNAs relay information about disease burden as a whole incorporating metabolic and inflammatory and cardiovascular details and follows standardised collection and analytical protocols but may also be less specific to renal pathology. [40] miRNAs in urine are more specific to renal injury since they originate in renal tissues. [41] They correlate with processes more local to the kidney such as fibrosis, inflammation and tubular damage. Use of urinary miRNAs provide insight for early diagnosis and monitoring of renal injury. The two levels of assessment are most powerful in concert reflecting systemic and organ-specific disease processes. [32]

8. Mechanistic Insights from Clinical-Pathological Correlation Studies

Correlation with Renal Histopathology

Variations in miRNA expression patterns and structural kidney injury. By means of clinical-pathological studies, a strong and established association with structural renal damage has been demonstrated for some miRNAs. Glomerulosclerosis is closely correlated to miR-21 (r≈0.65), implying that patients with greater glomerular scarring have more expression of this miRNA, whereas miR-146a is inversely correlated (i.e. greater levels of the miRNA are associated with no structural damage). [43] One prognosis factor can be already identified in the function of the miRNA. In relation to tubulointerstitial fibrosis, miR-21 is even better correlated (r≈0.72), implying a central role in regulating fibrogenesis. The inverse correlation of miR-146a with severity of fibrosis (r≈-0.64) reflects another possibility of function of the miRNA. [44] Podocyte injury is another important step in DKD progression and miRNA expression is

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implicated in that as well. Elevated levels of miR-21 correlated to reduced podocyte density seen by podocalyxin staining, whereas higher levels of miR-146a indicated preservation of podocyte integrity. [45]

Correlation with Inflammatory Infiltrates

Inflammatory cell infiltration is another element of DKD pathogenesis and miRNA expression closely mimics inflammation. miR-21 shows strong positive correlations with macrophage infiltration (or CD68 infiltration) with correlation coefficients going as high as 0.68. That highlight its role in the promotion of this inflammatory recruitment and activation. [26] Conversely miR-146a shows inverse correlations with macrophage/T-cell infiltration hence its role in inflammatory suppression. This "opposing" of miR-21 and 146 would again tie into the Yin Yang nature of miR-21 and mir-146a in DKD pathophysiology. [37]

Correlation with Molecular Markers

At a molecular level, miR-21 is associated with activation of essential fibrotic and inflammatory pathways. It positively correlates with TGF-β1 expression ($r \approx 0.75$) - a key mediator of fibrosis - as well as NF-κB activation and collagen IV deposition. This strengthens its role in promoting ECM accumulation and chronic inflammation. [38]

miR-146a, by contrast, is inversely correlated with TGF-β1 and NF-κB, acting as a negative regulator of inflammation and fibrosis. This duality highlights the relevance of examining both together for insight into disease mechanisms. [39]

9. Clinical Utility and Implementation

Proposed Diagnostic Algorithm

A clinically useful algorithm implementing miR-21 and miR-146a begins with prospectively screening patients with type 2 diabetes mellitus annually. Assessing these miRNAs allows for intimate insight into subclinical renal injury. The next step is calculating the ratio of miR-21/miR-146a by combining it as an indicator of risk. [30]

Patients with ratios below the threshold of 1.5 are at low risk status and should continue to be observed on a yearly basis. If patients are found to have an intermediate ratio somewhere between 1.5 and 2.5, they are moderate and may benefit from metabolic control efforts and starting renin–angiotensin system blockade. If the ratio is above 2.5 they are at high risk and should be referred to specialist nephrology for more intensive efforts to manage their disease. [31]

Other confirmatory tests with albuminuria and eGFR are still termed tests of choice, while some patients may require renal biopsy in select cases. Serial assessment of these miRNAs 6 months to 12 months will help to demonstrate the dynamic aspect of the progression of disease and therapeutic response. [42]

Clinical Decision Support

Incorporation of miRNA biomarkers into clinical decision-making offers advantages. They allow detection of DKD at a time when traditional markers such as albuminuria are normal, filling in a vital cancer in early diagnosis. They also enable identification of rapid progressors who can be targeted for early and robust intervention.[33]

MiRNA profiles may also help with selection of therapeutics. High levels of miR-21 may identify patients who would respond to renin–angiotensin system inhibitors; conversely low levels of miR-146a could potentially identify patients who would respond to anti-inflammatory approaches. Serial assessment of these biomarkers would provide real-time feedback on the adequacy of therapy.[34]

Integration with Current Guidelines

There is also growing awareness in recent clinical guidelines of the promise of novel biomarkers in DKD management, as evidenced by the recent KDIGO 2024 guidelines for the management of diabetes in chronic kidney disease, which underscore the potential of emerging biomarkers for enhanced risk stratification. The ADA Standards of Care (2025) also identify miRNAs as a promising resource, although widespread clinical usage remains in anticipation of further validation in larger studies from 2025 and beyond. Cardiovascular guidelines acknowledge the role of miRNAs as adjunct biomarkers for systemic risk assessments as well, thus highlighting a broader clinical significance.[35]

Practical Considerations

For successful implementation of miRNA based diagnostics, standard protocols for obtaining and storing samples, and measuring miRNAs must be established. Samples have been accrued from plasma, serum or urine, with EDTA plasma and urine being the most frequent sources used. Quantitative PCR is frequently used, both for routine clinical applications, with next-generation sequencing being a tool used more presently in academic studies, although point-of-care technologies are also in development. [46]

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Economically, the miRNA panel consisting of miR-21 and miR-146a is estimated to cost between $50-100, and could be reasonably comparable to biomarker based tests. Reimbursement also varies upon jurisdiction, and formal HTAs to rigorously inspect cost-effectiveness are needed. [47]

10. ctDNA Methylation and Epigenetic Resistance

ctDNA Methylation as a Biomarker

ctDNA methylation of circulating tumour DNA is a highly rich epigenetic marker that augments genomic ctDNA analysis, tracking regulatory changes in a gene expression context, rather than sequence-level mutations. In comparison to genomic changes, the amount of methylation in DNA is indicative of a more resilient set of markers in circulation, because one cannot as readily tear these fragments apart, nor disassociate it so easily, and so forth. Yet the greater tissue context is still available for retaining useful symbols therein, so CT DNA methylation still has features that can usefully participate in tissue identification. With analytical platforms such as bisulfite sequencing, methylation-specific PCR, and targeted methylation "panels" one arrives at the smorgasbord of ctDNA of different types, that let us pierce into the tapestry of methylation across them. It turns out that methylation burden (frequently referred to as methylation fraction), correlates with the tumour burden and so is informative for diagnostics and monitoring. ctDNA methylation is particularly useful in cancers with low mutational burden, or where genetic mutation does not capture the totality of tumour biology.[48]

Epigenetic Drivers of Resistance

Epigenetic changes serve as points of convergence for both intrinsic and acquired resistance to anticancer therapies. For example, transcriptional silencing of tumor suppressor genes through promoter hypermethylation can contribute to therapeutic resistance, such as MLH1 hypermethylation associated with resistance to specific chemotherapies or MGMT promoter methylation characterizing the sensibility of tumors to alkylators (like temozolomide). Within the context of DNA repair pathways, BRCA1 methylation promotes homologous recombination deficiency and 'sensitizes' cancer precursors to PARP inhibitors, resulting in DNA repair being rescued after this state of methylation is removed ultimately making treatment resistant. Epigenetic reprogramming allows lineage plasticity whereby tumors can adopt a different 'state' phenotype whilst losing their old one, like neuroendocrine transformation. Lastly, the intraspecies epigenetic heterogeneity encompasses different methylation states across tumor subclones may also confer resistance due to ready availability of different methylation states for a satellite population to adopt. [49]

Monitoring Epigenetic Resistance

Serial analysis of ctDNA methylation facilitates tracking of epigenetic changes in therapy, providing insight into the evolution of resistance in real time. Detection of new promoter hypermethylation events during therapy is suggestive of adaptive silencing of critical pathways while global hypomethylation signatures are often associated with genomic instability and aggressive tumour behaviour. New techniques such as cell-free methylated DNA immunoprecipitation (cfMeDIP), allow for cost-effective and high-throughput methylation profiling without requirement for bisulfite conversion, facilitating scalability to clinical use. Combining methylation profiling with genomic mutation profiling provides a deeper understanding of resistance, allowing tracking of genetic and epigenetic drivers. This is most important for resistance originating from non-mutational mechanisms which would not otherwise be detected. [40]

Epigenetic Therapies and ctDNA

The intersection of epigenetic therapies and ctDNA monitoring is an exciting area of interest for precision oncology. Hypomethylating agents like azacitidine and decitabine function by reversing abnormal DNA methylation patterns, ultimately reactivating inactivated tumour suppressor genes and restoring responsiveness to other treatment modalities. Analysis of ctDNA could provide insights into the dynamics of demethylation and resulting therapeutic response. Histone deacetylase inhibitors such as vorinostat and romidepsin further remodel chromatin and gene expression, often in combination with other drugs. Epigenetic priming refers to the concept that epigenetic therapies can increase the immunogenicity of tumours and these tumours can be rendered more sensitive to chemotherapy or immunotherapy as a result. ctDNA could serve as a valuable modality for tracking the changes in tumour methylation profiles that this phenomenon relies on. Resistance to epigenetic therapies can arise through mutation of regulators like DNMT3A or TET2, and ctDNA can allow for tracking of these evolutionary changes over time. [21]

10. Therapeutic Implications: miRNAs as Therapeutic Targets

Anti-miR-21 Therapies

The importance of miR-21 as a mediator of inflammation, fibrosis and maladaptive behaviour make it one of the most appealing targets for utilisation of RNA intervention in nephroprotection. Antisense oligonucleotide inhibition of miR-21 has shown promise

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in reducing renal injury in several experimental diabetic nephropathy models decreasing albuminuria, maintaining glomerular architecture, reducing mesangial expansion and tubulointerstitial fibrosis through restoration of protective targets such as PTEN, PDCD4 and TIMP3. This results in reduced overactivity of AKT in other conserved signalling pathways [61], leading to decreased maladaptive pro-survival signalling at the level of the cell and deposition of extracellular matrix. Anti-miR-21 strategies also dampens TGF-β activated pathways, the major molecular pathway involved in chronic diabetic renal injury. Of translational importance, RG-012, an anti-miR-21, have begun studies in humans for other fibrotic kidney diseases, and serve as proof of principle for subsequent development in diabetic kidney disease. From a precision medicine perspective, these may be therapies of preponderance in patients with significantly higher circulating or urinary miR-21 levels. [22]

miR-146a Replacement Therapy

In contrast to anti-miR-21 approaches, miR-146a replacement therapy is predicated on restoration of an endogenous anti-inflammatory and cytoprotective mechanism that is abrogated in diabetic kidney disease. Because miR-146a normally represses TRAF6- and IRAK1-dependent signaling upstream of NF-κB, downregulation of miR146a relieves a key regulatory brake on inflammation, oxidative stress, and fibrotic progression. Preclinical studies employing miR-146a mimics have demonstrated that replacement of miR-146a expression attenuates diabetic renal injury through reduction in inflammatory cytokine.production, suppression of macrophage recruitment and infiltration, and limiting oxidative stress with consequent decrease fibronectin deposition/ECM production. These interventions also led to preservation of renal structure and function, supporting the hypothesis that miR146a is more than just a biomarker of disease activity - it is an active determinant of renal resilience. The major challenge is in the realm of delivery. miR-146a mimics like all RNA therapeutics, would need to be effectively targeted to the kidney to be effective and to protect against rapid degradation and uptake by off-target tissues as well as avoiding activating indigenous immune responses. Notwithstanding, this modularmiR approach offers considerable conceptual strength, particularly where patients have a pronounced inflammatory phenotype with low endogenous miR-146a expression. [33]

Exosome-Based Therapeutics

Exosome-based platforms for delivery may offer one of the best approaches to overcoming the challenges of renal-targeted miRNA therapy. Exosomes are vesicles that shuttle RNA, protein and lipid from one cell to another, and in the body are naturally occurring, biologically compatible delivery vehicles. In diabetic kidney disease, exosomes can be engineered to carry anti-miR-21 molecules or miR-146a mimics to the renal tissues, combining biomarker-guided delivery with biologic delivery efficiency. Exosomes derived from mesenchymal stem cells are of interest because they contain naturally cargo that contributes to their anti-inflammatory and regenerative characteristics (including miR-146a), and possess renoprotective properties in preclinical models of diabetic nephropathy - for example attenuating fibrosis, improving kidney function, and modulating inflammatory drive (although purification from animal tissues and loading/loading efficiency are significant barriers that must be overcome before exosome therapeutics can be translated into popular clinical use). However, exosome-delivered miRNA may be the ultimate convergence of biomarker science, regenerative medicines and targeted drug delivery. [44]

Combination Strategies

Recognising the multifactorial nature of diabetic kidney disease, single-agent miRNA modulation strategies will not be optimal in all patients, thus combination strategies are particularly appealing. Early data from preclinical studies suggest that anti-miR-21 therapy may act in a synergistic manner with renin–angiotensin–aldosterone system (RAAS) blockade, through simultaneously decreasing the haemodynamic stress through reduced glomerular hyperfiltration, and supressing downstream signalling through decreases in renal microvascular fibrotic signalling. Similarly, miRNA-based interventions may complement SGLT2i therapies, which confer metabolic and haemodynamic renoprotection, but do not adequately normalise inflammatory or fibrotic pathways. Combining various miRNA modulation approaches with standard of care therapies may thus result in enhanced overall renal protection, delaying progression more than would be feasible with either strategy alone. This concept also allows for ‘personalised’ treatment selection. For instance, very high miR-21 expression patients may clearly justify anti-miR-21 therapy, whilst patients with markedly decreased miR-146a expression may be more suited to replacement strategies. Such biomarker based approaches to therapeutically matching individual patients is one of the components of the personalised theragnostic model of diabetic kidney disease care. [45]

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11. Challenges and Future Directions

Standardization and Harmonization

One challenge hampering clinical adoption of miRNA biomarkers is a lack of standardization throughout the entire testing process. Preanalytical variability is significant, such that type of collection tube, centrifugation, storage time, and freeze–thaw handling can all affect observed miRNA levels. Then analytical variation compounds the problem. RNA extraction, normalization procedures, target assay chemistry, and inter-assay precision all differ from lab to lab. Currently there is no standardized model of reference ranges for miR-21 and miR-146a in diabetic cohorts, nor are there international external quality assessment schemes for these and other miRNA biomarkers that are widely used. For miRNA testing to become clinically viable, harmonized protocols and standards of proficiency will need to be established. [36]

Biological Variability

Biological variability poses further challenges. The levels of circulating and urinary miRNAs have been shown to be affected by circadian rhythms, age and sex, metabolic status, comorbidity, medications, and potentially lifestyle factors, suggesting that even biologically relevant biomarkers may vary markedly in the absence of disease progression unless the sampling approach is fully harmonized. The degree of tissue specificity may also differ between biofluids: in circulation, the miRNAs may act as signals from many organ systems, while urinary miRNAs are relatively more kidney-specific but still influenced by overall hydration status and the conditions under which urine is handled. Moreover, "expression" of miRNAs is not static, but may change over the course of disease progression or in response to therapy; this strengthens the argument for serial monitoring rather than one-off measurements, but complicates interpretation and threshold definitions. [37]

Large-Scale Validation

Though the evidence so far for miR-21 and miR-146a is substantial, large-scale validation is still required before we will accept them into routine practice. Future studies need to involve multicenter cohorts, with tracking of longer term outcomes and patients of diverse ethnicities and geographical backgrounds to demonstrate generalizability. Direct comparison with other emerging classes of biomarker, including proteomic and metabolomic panels, will be required to determine if there is truly incremental value in miRNA based strategies, or alternatively if they are best utilized in conjunction with other molecular tools. Another area of research need is in cost-benefit analysis; real value of such strategies in miRNA-guided management will hinge not only on diagnostic performance, but also on demonstrating improvements in outcomes in a cost-effective manner. [48]

Regulatory Pathway

The regulatory landscape of miRNA biomarkers and therapeutics is still evolving and miR-21 and miR-146a need validation through rigorous qualification by the FDA, EMA and other agencies (eg analytical validity, clinical validity, and clinical utility, companion diagnostic approval) if these miRNAs are to gain traction as clinically actionable biomarkers in diabetic kidney disease. Laboratory developed tests should also have clear reigns and standards for quality control to provide consistency amongst providers. More than regulatory approval is needed however, there also needs to be established pathways for reimbursement through the health technology assessment process, as implementation depends on whether payers acknowledge clinical value. [44]

12. Conclusions

Summary of Key Evidence

Cumulatively, this evidence implicates miR-21 and miR-146a as mechanistically informative biomarkers in DKD. miR-21 is consistently elevated in circulation and urine of DKD patients, outperforms statistically as a diagnostic biomarker, correlates with albuminuria, eGFR rates of decline, histopathologic injury and inflammation-fibrosis, and predicts disease progression, ESKD, and mortality. On the other hand, miR-146a is consistently reduced, correlates inversely with disease associations such as eGFR and albuminuria, marks a 'lost control' of anti-inflammatory signalling, and provides strong prognostic associations. Panels combining either biomarker outperformed both alone, and the miR-21/miR-146a ratio is a biologically satisfying measure of net inflammatory-fibrotic burden. Beyond their roles as biomarkers, the functional relevance of miR-21 and miR-146a as therapeutic targets is clear, and both anti-miR-21 and miR-146a replacement strategies have shown exciting effects in preclinical models of disease.

Clinical Implications

The potential clinical implications of these findings are clear: miRNAs could represent a non-invasive stable biomarker that enhances the biologic interpretation of markers of kidney injury, such as albuminuria and eGFR. Earlier detection of diabetic kidney disease may be possible, especially in the normoalbuminuric patients who are missed by current screening programs. They may help identify rapid progressors who should be referred at an earlier timepoint for more marked intervention decisions. miRNA profiles might be used to

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direct the choice and intensity of therapies, provide serial measurements for monitoring treatment response, and enrich clinical trials in kidney diseases by selecting biologically high risk participants. One could thus envisage a precision nephrology model where miRNAs would fit naturally.

Research Priorities

The areas of research priority are prospective multicenter validation, assay harmonization, and integration with other biomarker strategies. Future work should determine how well miRNA panels as above function alongside proteomic, metabolomic, and genetic risk based markers, and whether integrated models outperform standards of care. Interventional trials are also needed to determine whether miRNA guided management leads to better renal and cardiovascular outcomes than management using standard of care therapy. Last, qualification will be of critical importance if such biomarkers are to be moved from being research tools into the practice of Nephrology.

The Road Ahead

The incorporation of circulating and urinary miRNAs into the routine management of diabetic kidney disease may be through comprehensive biomarker platforms that enable earlier diagnosis, risk stratification in patients for treatment selection and progress monitoring. Gradual advances in technology may lead to point-of-care miRNA testing so that decentralized and scalable screening becomes viable even in limited resource settings. Simultaneously, the presence of miRNAs as both biomarkers and targets means that a theragnostic option is available in which the molecular signal enables identification of disease while similarly being used to guide the treatment and monitoring process. If successfully validated and implemented, this strategy could lead to a major global impact enabling earlier and more personalised, and therefore more effective management of diabetic kidney disease.

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