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Study of Serum microRNA-217 Expression Pattern in Different Stages of Diabetic Kidney Disease – a Cross-sectional Study

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ABSTRACT

Background: Diabetic kidney disease (DKD) represents the leading cause of end-stage renal disease worldwide, affecting 30-40% of patients with type 2 diabetes mellitus (T2DM). Some microRNAs (miRNAs), like miRNA-217 are upregulated in Diabetic Kidney Disease (DKD), and known to play a key role in Diabetes Mellitus & its complications. Recent studies have shown miRNA 217 to be involved in the development of DKD, by promoting renal inflammation, angiogenesis and fibrosis.

Aim and objectives: To assess the miR217 expression levels in DKD patients with differing stages of albuminuria, compared to normoalbuminuric Diabetes mellitus -II patients & to identify its role as a predictive biomarker of DKD.

Methodology: This analytical cross-sectional study recruited 135 participants aged 40-65 years from a Govt medical college Hospital in Tamil Nadu. Participants includedT2DM patients (n=34) & DKD patients & healthy controls(n=35). Fasting serum samples were collected & miRNA-217 extraction and qRT-PCR quantification was done & Fold change was calculated, along with the baseline clinical parameters (age, BMI, HbA1c, lipids, urea, creatinine, eGFR, UACR).

Statistical analyses like Kruskal-Wallis tests, Spearman's correlations & ROC curves were computed using Jamovi software version 2.6.44

Results: Serum miRNA-217 expression was markedly elevated in DKD patients with microalbuminuria (39.36 ± 76.24 fold change) & macroalbuminuria (64.32 ± 109.23 fold change) compared to Diabetes mellitus -II patients with normoalbuminuria (2.29 ± 4.77, P=0.027).MiRNA-217 correlated positively with UACR (ρ=0.472, p<0.001) and was able to discriminate DKD from Diabetes-II, with 59% sensitivity & 90% specificity, ROC analysis yielded AUC 0.738 (p<0.001).

Conclusion: Serum miRNA-217 exhibits progressive up-regulation in accordance with stages of DKD severity, with moderate diagnostic utility. miRNA-217 could be a potential biomarker for early DKD detection and risk stratification, warranting longitudinal studies in larger populations for further validation and establishment of these findings.

Keywords: microRNA 217, miRNA 217, Diabetic Kidney Disease, DKD, UACR.

Introduction

Diabetic Kidney Disease (DKD) is a microvascular complication affecting 30–40% of patients with diabetes, and it is the leading cause of chronic kidney disease and end-stage renal disease (ESRD) worldwide (1,2). DKD develops through complex pathogenic mechanisms triggered primarily by sustained hyperglycemia, which induces metabolic and hemodynamic alterations, including glomerular hyperfiltration, glomerulosclerosis, tubulointerstitial inflammation, and fibrosis (2,3).

MicroRNAs (miRNAs) are endogenous, small non-coding RNAs that regulate gene expression post-transcriptionally by targeting messenger RNAs. They play crucial roles in maintaining cellular homeostasis and are involved in various biological processes, such as proliferation, differentiation, and immune response regulation. Dysregulation of miRNAs contributes to the development and progression of several diseases, including cardiovascular diseases, cancer, autoimmune disorders, infectious diseases, Diabetic Kidney Disease (DKD), and neurodegenerative conditions. Their altered expression can serve as diagnostic biomarkers and therapeutic targets, highlighting their potential in disease diagnosis and treatment strategies (4–7).

Many microRNAs have been implicated in the pathogenesis and progression of DKD, though with varying results. One such microRNA, miRNA-217, has been identified to play a crucial role in the pathogenesis and progression of DKD. miRNA-217 is found to promote angiogenesis and renal fibrosis by inhibiting the expression of SIRT1, a protein that protects against oxidative stress, apoptosis, and fibrosis, thereby leading to the development of DKD (8).

Upregulation of miR-217 expression could be an important molecular mediator in DKD, and increasing levels could indicate the progression of disease (9). There are very few human studies on miR-217 levels in Diabetic Kidney Disease carried out in the Indian population. This study is an attempt to identify the variations in miR-217 levels in different stages of severity of DKD and to assess its diagnostic utility as a candidate biomarker for DKD in a small population in South India.

Methods

Study Design and Participants

This is an analytical cross-sectional study conducted in 135 participants aged 40–65 years attending the Diabetology OPD in a Government Medical College Hospital in Salem, Tamil Nadu. The study included 35 healthy non-diabetic controls with normal renal function and 100 patients with type 2 diabetes mellitus (T2DM) categorized by urinary albumin/creatinine ratio (UACR) into normoalbuminuria (<30 mg/g, n=34), microalbuminuria (30–300 mg/g, n=33), and macroalbuminuria (>300 mg/g, n=33).

Patients with type 2 Diabetes Mellitus and Diabetic Nephropathy were included in the study. Healthy non-diabetic controls without any comorbid illness formed the control group. Individuals with malignancies, chronic renal, liver, or cardiac diseases, urinary tract infections, renal stones, recent nephrotoxic drug use, co-existing comorbid conditions such as ischemic heart disease, hypertension, other diabetic complications, or recent NSAID or hormonal treatment were excluded from the study. Institutional Ethical Committee approval was obtained prior to the commencement of the study, and written informed consent was obtained from all participants before enrollment.

Laboratory Analysis

Fasting blood and urine samples were collected. Five millilitres of venous blood were drawn from each participant and divided into two parts: one for biochemical tests and the other for RNA extraction. Two millilitres were collected in fluoride-containing tubes, another 2 mL in EDTA-containing tubes, and the remaining portion was left for 10 minutes to clot and then centrifuged at 3000 rpm for 5 minutes. The first part for biochemical tests was used immediately, while the second part was stored for miRNA detection. Serum was separated and stored in RNase/DNase-free tubes at −80°C until RNA isolation.

Clinical and laboratory assessments included comprehensive demographic data collection, including age, sex, and relevant medical history. Renal function was evaluated using the estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI formula, and the urinary albumin-to-creatinine ratio (UACR) was measured from spot urine samples to classify the stages of diabetic nephropathy. Additional biochemical parameters assessed included fasting blood glucose, HbA1c, lipid profile, serum urea, and creatinine levels using the fully automated analyzer (EM200) and HbA1c analyzer (TOSOH).

MiRNA Extraction (Qiagen Kit)

MiRNAs were isolated using a miRNA extraction kit. The collected serum was mixed with 300 µl of binding buffer solution, and then ethanol was added to precipitate total RNA and eluted in nuclease-free water. Total RNA was then incubated with miRNA wash solutions without preamplification, and purified small RNA molecules were eluted in 50–100 µl of sterile RNase-free water supplied with the kit. The samples were stored at −80°C until used.

Primer Design and Positive Controls

Three primers were designed each for miR-217 and miR-423-5p, which was used as an endogenous control. One forward primer (5'-AACACGTGTACTGCATCAGGAAC-3'), Universal reverse primer (5'-GCGAGCACAGAATTAATACGAC-3'), Universal reverse transcriptase primer (5'-GCGAGCACAGA ATTAATACGACTCACTATAGGTTTTTTTTTTTVN-3'). Synthetic oligonucleotides for miR-217-5p and miR-423-5p were ordered for optimization.

cDNA Synthesis and miR-217 Amplification

After RNA extraction, samples were converted into cDNA using the PolyA method, employing PolyA enzyme, RT enzyme, and universal RT primer. Quantitative real-time polymerase chain reaction (qRT-PCR) was employed to quantify miRNA-217 levels using specific primers and BioRad SsoAdvanced SYBR Green Supermix on a QuantStudio 8 RT-PCR system. Normalization was performed using the endogenous control miRNA-423-5p to correct for expression levels across the control and DKD groups (10). Fold change of miR-217 in all samples was calculated using the Livak method 2^(−ΔΔCt) (11). Quality control included assessment of RNA concentration and purity by spectrophotometry (NanoDrop method) and verification of PCR efficiency and specificity through melt curve analysis.

Statistical Analysis

Descriptive statistics of baseline parameters and group comparisons of miR-217 and other parameters were performed using non-parametric tests (Kruskal-Wallis), which are appropriate given the non-normal distribution of miRNA fold-change data. Correlation analyses employed Spearman's rank

correlation to evaluate associations between miRNA-217 levels and clinical parameters such as UACR and glycemic indices. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of miRNA-217 as a diagnostic biomarker of Diabetic Nephropathy. Data analysis was performed using Jamovi software version 2.6.44. A post-hoc power analysis was conducted using the observed AUC of 0.738, with $\alpha = 0.05$ and a case-to-control ratio of 66:34 (DKD:DM-II), which yielded a post-hoc power of approximately 80%, suggesting adequate statistical power to detect the observed diagnostic effect for the primary biomarker outcome.

Table 1 Baseline Characteristics of the Study Participants

S. No	Parameter	Healthy Controls (Mean ± SD)	Diabetes Mellitus-II (Mean ± SD)	Diabetic Kidney Disease (Mean ± SD)
1	N	35	34	66
2	Age (years)	51.27 ± 10.75	52.91 ± 10.29	56.35 ± 9.59
3	BMI	23.21 ± 5.28	26.37 ± 4.95	24.41 ± 5.10
4	Duration of Diabetes	—	5.86 ± 5.7	7.52 ± 7.0
5	FBS (mg/dl)	79.73 ± 16.47	159.79 ± 79.26	173.42 ± 87.70
6	HbA1c (%)	5.54 ± 0.85	8.60 ± 2.25	8.77 ± 2.64
7	Urea (mg/dl)	25.03 ± 5.82	24.58 ± 9.14	29.72 ± 17.94
8	Creatinine (mg/dl)	0.93 ± 0.18	1.09 ± 0.37	1.40 ± 0.76
9	T. Cholesterol	172.17 ± 31.59	184.84 ± 50.13	174.4 ± 48.29
10	Triglycerides	158.52 ± 67.77	175.98 ± 90.58	184.70 ± 96.19
11	HDL	41.07 ± 7.83	47.79 ± 30.68	44.06 ± 9.85
12	LDL	99.40 ± 32.89	115.82 ± 43.82	94.02 ± 39.41
13	eGFR (ml/min)	80.60 ± 22.25	70.06 ± 15.52	60.63 ± 24.04
14	UACR	13.55 ± 9.19	15.14 ± 8.3	1087.8 ± 2320.22
15	miRNA-217 expression	—	2.29 ± 4.77	46.70 ± 87.38

Results

Participant Characteristics and Baseline Parameters

The study included 35 healthy controls, 34 patients with Diabetes Mellitus-II (DM-II), and 66 patients with Diabetic Kidney Disease (DKD) who were further divided into those with microalbuminuria (n=33) and macroalbuminuria (n=33), totalling 135 participants. The mean age of the participants was 54.1 years and all groups were age-matched (p=0.15). The baseline characteristics of the Diabetes Mellitus-II and DKD groups are presented in Table 1. The glycemic indices — fasting blood sugar (FBS) and HbA1c — were significantly different among all four groups (p<0.001), as shown in Figure 1. Similarly, the renal parameters — urea and creatinine — were significantly different among the groups (p=0.006, p<0.001, respectively). The estimated glomerular filtration rate (eGFR) was significantly lower in patients with DKD, with the most pronounced decline observed from the normoalbuminuria to the macroalbuminuria group (p<0.001). While lipid parameters such as total cholesterol and LDL were significantly different among the groups (p=0.002, p<0.001), serum HDL and BMI showed no significant change, as given in Table 2.

MiRNA-217 Expression in Diabetes Mellitus-II and DKD

In patients with DKD, miRNA-217 expression increased progressively from the normoalbuminuria to the macroalbuminuria group (Table 2), the difference being statistically significant (p=0.008). miRNA-217 expression (fold change) was significantly elevated in DKD patients with microalbuminuria (39.36 ± 76.24 fold change) versus Diabetes Mellitus-II patients with normoalbuminuria (2.29 ± 4.77, p=0.027), and among DKD patients with macroalbuminuria (64.32 ± 109.23 fold change) versus Diabetes Mellitus-II patients with normoalbuminuria (2.29 ± 4.77, p=0.017). No significant difference was found between the micro- and macroalbuminuria groups (p=0.803). The large standard deviations relative to the mean miRNA-217 fold-change values are reflective of the inherent inter-individual biological variability in circulating miRNA expression, which is well-documented in serum miRNA biomarker studies and is a recognized characteristic of miRNA quantification in heterogeneous clinical populations (21,23).

Table 2 Comparison of miR-217 and Other Parameters Across Study Groups

S. No	Parameters	Healthy Controls (Mean ± SD)	DM-II Normoalbuminuria (Mean ± SD)	DKD Microalbuminuria (Mean ± SD)	DKD Macroalbuminuria (Mean ± SD)	P-value
1	Age (years)	51.27 ± 10.75	52.91 ± 10.29	56.02 ± 9.70	56.21 ± 9.57	0.15
2	BMI	23.21 ± 5.28	26.37 ± 5.00	24.34 ± 5.64	24.59 ± 3.76	0.070
3	Duration of Diabetes	—	5.86 ± 5.7	7.43 ± 7.16	7.75 ± 6.76	0.017
4	FBS (mg/dl)	79.73 ± 16.47	159.79 ± 79.26	161.63 ± 81.30	201.95 ± 98.04	<0.001
5	HbA1c (%)	5.54 ± 0.85	8.60 ± 2.25	8.41 ± 2.66	9.62 ± 2.48	<0.001
6	Urea (mg/dl)	25.03 ± 5.82	24.58 ± 9.14	25.57 ± 10.96	39.79 ± 26.31	0.006
7	Creatinine (mg/dl)	0.93 ± 0.18	1.09 ± 0.37	1.21 ± 0.51	1.85 ± 1.04	<0.001
8	T. Cholesterol	166.07 ± 21.84	172.77 ± 30.05	176.48 ± 39.10	214.17 ± 49.56	0.002
9	Triglycerides	158.52 ± 67.77	175.98 ± 90.58	176.84 ± 81.31	203.32 ± 125.3	0.784
10	HDL	41.07 ± 7.83	47.79 ± 30.68	43.78 ± 8.84	44.74 ± 12.16	0.546
11	LDL	92.95 ± 25.54	98.45 ± 37.61	101.96 ± 32.80	132.88 ± 32.84	<0.001
12	eGFR (ml/min)	80.6 ± 22.25	70.06 ± 15.52	66.9 ± 23.25	45.47 ± 19.01	<0.001
13	UACR	13.55 ± 9.19	15.14 ± 8.3	101.15 ± 64.77	3476.5 ± 3258.8	<0.001
14	miRNA-217 expression	—	2.29 ± 4.77	39.36 ± 76.24	64.32 ± 109.23	0.008

Table 3 ROC Curve Summary

	AUC	Std. Error	95% CI Lower	95% CI Upper	P
miRNA-217	0.738	0.0658	0.609	0.867	<0.001

Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden's Index
2.95	59%	90%	92%	52.94%	69.5%	0.490

Non-parametric statistical tests were therefore employed throughout, as these do not assume normality of distribution and are robust to such variability. miRNA-217 expression showed a strong positive correlation with UACR (Spearman's rho = 0.472, p<0.001), indicating a significant association with increasing albuminuria severity (Table 3).

miRNA-217 as a Diagnostic Biomarker of DKD

ROC curve analysis for miRNA-217 showed an area under the curve (AUC) of 0.738 (95% CI: 0.609–0.867, p<0.001), indicating moderate to good diagnostic accuracy for distinguishing between DKD and Diabetes Mellitus-II without DKD. At a cut-off of 2.95 fold change, miRNA-217 demonstrated 59% sensitivity, 90% specificity, 92% positive predictive value (PPV), and 52.94% negative predictive value (NPV), with an overall accuracy of 69.5%. While the sensitivity of 59% is modest, the high specificity of 90% and PPV of 92% suggest that miRNA-217 may be particularly valuable as a confirmatory or rule-in biomarker when used adjunctively alongside established clinical markers such as UACR and eGFR, rather than as a standalone screening test.

Discussion

The present study was conducted in a small South Indian population with 135 participants, consisting of 35 healthy non-diabetic controls (Group 4), 34 individuals with Diabetes Mellitus-II (Group 1 — normoalbuminuria), and 66 individuals with DKD further divided into Group 2 (microalbuminuria, n=33) and Group 3 (macroalbuminuria, n=33).

In this cross-sectional study, serum miRNA-217 was significantly upregulated in the micro- and macroalbuminuria groups compared to those with normoalbuminuria (p=0.008) and showed a positive correlation with UACR (p<0.001), implicating its plausible relationship with albuminuria status. Our findings are similar to those of Shao et al., who proposed that serum miR-217 levels steadily increased in individuals presenting with microalbuminuria and macroalbuminuria compared to those with normoalbuminuria (9). Although the glycemic indices — fasting blood glucose (FBG) and HbA1c — were significantly elevated in participants with Diabetes Mellitus and Diabetic Kidney Disease compared to healthy controls (p<0.001), they did not correlate with miR-217 levels.

It is acknowledged that diabetes duration showed a significant difference across groups (p=0.017), representing a potential confounder. However, given the limited sample size of this study, formal multivariable regression analysis incorporating multiple covariates was not feasible. Age, on the other hand, was not significantly different across the four groups (p=0.15, Table 2), thereby minimizing its confounding potential. Future studies with larger sample sizes should incorporate multivariable regression models to adjust for duration of diabetes and other potential confounders.

miRNA-217 has been implicated in the pathogenesis of Diabetic Kidney Disease by inactivating sirtuin 1 (SIRT1), a member of the silent information regulator 2 family of NAD-dependent deacetylases that function as transcriptional regulators (12). Gene polymorphisms in the gene encoding Sirtuin 1 have been found to be associated with the development of Diabetic Nephropathy (13,14). Many mechanisms have been proposed to explain the renoprotective role of SIRT1. Hasegawa et al. reported that downregulation of SIRT1 upregulates the expression of Claudin-1 protein, thereby contributing to albuminuria in DKD (15,16). Claudin-1 is an integral component of the tight junction, and an increase in its levels results in podocyte effacement and albuminuria (17). miR-217 has been found to directly act on the 3'UTR of the SIRT1 gene and significantly inhibit the expression of SIRT1, thereby acting as a negative regulator of SIRT1 (18). This explains the probable mechanism underlying our findings of upregulation of miR-217 in patients with both micro- and macroalbuminuria, while showing no change in normoalbuminuric Diabetes patients.

SIRT1 also deacetylates and inactivates Hypoxia-Inducible Factor-1α (HIF-1α), which plays a significant role in promoting renal fibrosis and renal sclerosis (19). Shao et al. showed that miRNA-217 is markedly upregulated, leading to suppression of SIRT1, activation of HIF-1α, and subsequent induction of profibrotic and pro-inflammatory mediators including CTGF, endothelin-1, fibronectin, TGF-β1, and VEGF; while gene silencing of miRNA-217 attenuated these responses (20). These observations provide evidence that miRNA-217 is an upstream regulator of the SIRT1/HIF-1 axis, a pathway implicated in tubular hypoxia, interstitial fibrosis, and albuminuria seen in Diabetic Nephropathy (19,21). Similar work in podocytes has demonstrated that high-glucose conditions elevate miRNA-217 and that specific inhibition of miRNA-217 restores PTEN expression, enhances autophagic flux, and mitigates podocyte injury and insulin resistance (7).

The present findings suggest that serum miRNA-217 expression increases with advancing albuminuria, along with a significant decline in eGFR from the normoalbuminuric DM-II group to the DKD group with macroalbuminuria (p<0.001) and between the micro- and macroalbuminuria groups (p=0.005). However, no significant correlation was found between miR-217 and eGFR. According to Loredana Fiorentino et al., miRNA-217 was found to be upregulated in diabetic mouse kidneys and mesangial cells treated with high glucose (22). miRNA-217 has been found to be increased in DKD patients and was positively correlated with ln(albumin-creatinine ratio), HbA1c, HOMA-IR, and HIF-1α, while showing a negative correlation with SIRT1 (9).

The large standard deviations observed in miRNA-217 fold-change values across all groups are consistent with the well-documented inter-individual biological variability inherent to circulating miRNA measurements in clinical populations (21,23). This variability is further attributable to differences in disease heterogeneity, metabolic status, and comorbid burden among participants. The use of non-parametric statistical methods (Kruskal-Wallis and Spearman's correlation) was specifically chosen to account for this non-normal distribution, and results were statistically significant despite this variability, underscoring the robustness of the observed associations.

Given the cross-sectional design of this study, the term "predictive biomarker" has been intentionally avoided throughout the revised manuscript. miRNA-217 is herein described as a diagnostic biomarker and a candidate for risk

stratification. The observed 59% sensitivity, while modest for a standalone screening tool, is complemented by the high specificity of 90% and PPV of 92%, suggesting that miRNA-217 may function best as a confirmatory or adjunct biomarker in combination with established clinical markers such as UACR and eGFR. These findings are exploratory in nature and require validation in prospective longitudinal studies.

To assess the role of miRNA-217 as a diagnostic biomarker of DKD, ROC curve analysis was performed, which showed that serum miRNA-217 could discriminate DKD from T2DM without nephropathy ($p<0.001$) with moderate sensitivity and high specificity. As the miR-217 levels correlate with DKD severity, its levels could be utilized for the early detection and monitoring of DKD progression, enabling timely clinical intervention. This study emphasizes the important role played by miRNA-217 in the pathophysiology of DKD, highlighting its potential as an emerging diagnostic biomarker. Given the very limited number of human studies relating miR-217 to DKD, the present findings could represent an important milestone in advancing miRNA research directed towards DKD diagnosis and management. These results require validation in further longitudinal studies in larger populations.

Limitations

The limitations of the present study include the smaller sample size, absence of an a priori power calculation, lack of longitudinal follow-up of Diabetes and DKD patients, and the inability to perform multivariable regression analysis to adjust for potential confounders such as diabetes duration due to the limited sample size. Furthermore, the cross-sectional design precludes any causal or temporal inference regarding the role of miRNA-217 in DKD progression. The modest sensitivity of 59% limits its standalone clinical application as a screening biomarker.

Scope for Future Study

Prospective longitudinal studies in larger populations are warranted to validate the diagnostic utility of serum miRNA-217 in DKD. Multivariable regression analyses adjusting for key confounders including diabetes duration, hypertension, and medications should be incorporated. SIRT1 levels can be measured and their relationship with miR-217 expression in type 2 Diabetes and DKD patients can be assessed to further elucidate the mechanistic pathway.

Conclusion

Serum miRNA-217 levels have been found to be upregulated in type 2 diabetes patients and increase progressively with DKD severity, correlating positively with albuminuria — a key marker of kidney damage. With only a few studies available, the present study is an attempt to assess the role of miR-217 in DKD as a diagnostic biomarker, while future studies in larger populations are needed to establish its exact role in DKD pathogenesis. Once proven, miRNA-217 silencing could prove to be a novel therapeutic strategy to alleviate the inflammation and fibrotic changes seen in DKD, thereby extending the treatment protocol beyond conventional glycemic and blood pressure control. This targeted approach appears promising and could arrest or slow kidney damage and improve clinical outcomes in patients with Diabetic Nephropathy.

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