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Original Article

Evaluation of the role of plasma glycated CD59 and FRMD3 variants as predictors of diabetic nephropathy

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Abstract

Plasma glycated CD59 (gCD59) is evaluated as a predictor for diabetic nephropathy (DN), and the association between FRMD3 gene mutations and DN susceptibility in type 2 diabetes (T2D) patients is explored. This cross-sectional study included 320 patients with type 2 diabetes mellitus (T2DM), divided equally into two groups: those with and without microalbuminuria. Plasma gCD59 levels were measured using a sandwich ELISA, and FRMD3 gene mutations were identified via PCR and Sanger sequencing. Statistical analyses assessed biomarker levels and their association with DN. Plasma gCD59 levels were significantly higher in patients with microalbuminuria (mean 711.27 pg/mL) compared to those without (mean 424.06 pg/mL). The G allele of the FRMD3 gene was more prevalent in DN patients (51.7% *versus* 41.2%), with the GG genotype showing a strong association with DN. Plasma gCD59 and FRMD3 gene polymorphisms are promising biomarkers for the early detection of DN in T2DM patients. Integrating these markers into routine clinical assessments may enhance early diagnosis and facilitate the development of personalized management strategies.

Keywords: diabetic nephropathy, plasma glycated CD59, FRMD3 gene polymorphisms, type 2 diabetes mellitus, microalbuminuria, kidney disease biomarker

Introduction

Diabetic nephropathy, initially described as intercapillary glomerulonephritis by Wilson and Kimmelstiel in 1936 [1], is a severe kidney disorder associated with prolonged high blood sugar levels. Nephrotic syndrome symptoms, including significant proteinuria, hypertension, and a gradual decline in kidney function characterize this condition. In its severe forms, diabetic nephropathy can progress to kidney failure, leading to end-stage renal disease (ESRD) and necessitating dialysis or kidney transplantation.

Clinically, diabetic nephropathy (DN) is identified by overt nephropathy, marked by proteinuria exceeding 0.5 grams per 24 hours [2]. Discoveries in the early 1980s indicated that even minimal levels of albumin in the urine, often undetectable by conventional methods, could predict the future onset of proteinuria in both type 1 and type 2 diabetes, a stage known as microalbuminuria or incipient nephropathy [3–5]. The incidence of proteinuria varies, occurring in approximately 15–40% of individuals with type 1 diabetes (T1D) and affecting 5–20% of patients with type 2 diabetes (T2D) [6–10]. DN prevalence is notably higher among certain racial and ethnic groups, including African Americans, Asians, Hispanics, and Native Americans, particularly Mexican-Americans. In Pima Indians, for example, DN is observed in about 50% of all diabetic patients [11].

The increased prevalence of type 2 diabetes and the improved longevity of these patients have resulted in more individuals progressing to ESRD, requiring renal

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replacement therapy. In the United States, approximately 40% of new ESRD cases are attributed to DN [12]. Despite 20–30% of patients with either T1D or T2D showing nephropathy symptoms, a smaller fraction of those with T2D progress to ESRD. However, given the higher prevalence of T2D, these patients constitute over half of all new dialysis cases.

In India, it is estimated that around 77 million adults aged 18 years and older suffer from T2D, with nearly 25 million classified as prediabetic, placing them at a higher risk of developing the disease soon. More than half of these individuals are unaware of their condition, which can lead to severe health complications if diabetes remains undetected and untreated [13]. Early detection and timely intervention are critical to managing and potentially preventing the complications associated with diabetes.

The clinical progression of diabetic nephropathy in type 1 diabetes (T1D) typically advances through five stages, from hyperfiltration and hypertrophy in Stage I to end-stage renal disease in Stage V. In type 2 diabetes (T2D), these stages are less clearly defined but follow a similar progression [14]. Recent research has highlighted that factors such as prolonged hyperglycemia, advanced glycation end products, activation of protein kinase C (PKC), increased production of transforming growth factor β, and oxidative stress play significant roles in the development of diabetic nephropathy [7, 8]. Additionally, the activation of the complement system, particularly through the formation of the membrane attack complex (MAC), has been implicated in the progression of the disease [9, 10]. While effective at eliminating pathogens, MAC formation can also damage the body's own cells, leading to complications like thrombosis. The glycation-inactivation of the complement regulatory protein CD59 has been linked to the pathophysiological processes in diabetic nephropathy [15–17].

This study sought to establish plasma glycated CD59 (gCD59) as a reliable biomarker for predicting DN, which could have profoundly influenced clinical practice. By facilitating early risk stratification, this biomarker enabled personalized interventions that improved patient outcomes. Successful validation of plasma gCD59 could have greatly enhanced the management of DN and contributed to advancements in precision medicine within diabetes care. This study aimed to clinically validate the efficacy of plasma gCD59 in predicting nephropathy in type 2 diabetes (T2D) patients. Moreover, it explored the potential link between FRMD3 mutations and DN, enhancing our understanding of the genetic factors that may predispose individuals to renal complications. The objective was to evaluate the relationship between plasma glycated CD59 levels and the presence of FRMD3 gene mutations, providing a comprehensive insight into the predictive factors associated with renal complications in these patients.

Material and methods

Study design and sample size calculation

This case-control cross-sectional study included a cohort of individuals with T2D, both with and without nephropathy. Based on a type I error of 0.05 and a power of 80%, the calculated sample size required was 160 subjects (American Diabetes Association Guidelines).

Recruitment and inclusion/exclusion criteria

A total of 320 diabetic individuals were recruited, divided into two groups: 160 patients with microalbuminuria (ACR <300 mg/g) and 160 without (ACR <300 mg/g), all with HbA1C levels greater than 6.5%. Patients with other medical conditions, such as infections, hypertension, or cardiovascular issues, were excluded to minimize confounding factors.

Demographic data collection

Demographic and clinical data, including age, sex, family history, BMI, diabetes status, hypertension, microalbuminuria, HbA1c, and creatinine levels, were collected. Height and weight were measured for BMI calculation, and clinical details were extracted from medical records (due to word limit, details are not provided). Diabetes and hypertension were diagnosed based on fasting plasma glucose levels and average blood pressure measurements, respectively.

Sample collection and processing

Blood samples were collected after a 12-hour fast using EDTA and plain vacutainer tubes. Serum and plasma were separated by centrifugation at 3000 rpm for 10 minutes, aliquoted, and stored at -80°C until analysis.

Laboratory analysis

Plasma levels of gCD59 were quantitatively analyzed using a sandwich ELISA method (Product# SEB336Hu,

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USCN Life Science Inc., Wuhan, China). The assay was performed per the manufacturer's guidelines, with optical density measured at 450 nm to determine the concentration of CD59 based on a standard curve. Additionally, genomic DNA was extracted from blood samples using the salting-out method [18], and PCR was used to amplify specific regions of the FRMD3 gene for mutational analysis [19].

PCR and mutational analysis

PCR amplification targeted exons 16 and 17 of the FRMD3 gene, with oligonucleotide primers synthesized for this purpose. Post-PCR, products were visualized on a 2% agarose gel and subjected to automated Sanger sequencing to identify mutations with the FRMD3 gene rs39075 primers.

Quantitative and qualitative DNA analysis

The quantity and quality of extracted DNA were assessed using a Nanodrop instrument, with absorbance ratios at 260 nm and 280 nm indicating purity. The DNA was then used for further PCR-RFLP and sequencing analyses to explore potential links between FRMD3 mutations and DN.

Sequence analysis

For DNA sequence analysis, the PCR products were processed using a Taq-Dye deoxy terminator cycle sequencing kit (Applied Biosystems) and analyzed with an automated ABI 3730 sequencer. Both forward and reverse primers were employed for sequencing. The obtained sequences were analyzed using the NCBI BLAST software program to identify potential mutations. Reference sequences were sourced from the National Center for Biotechnology Information (NCBI) of the NIH and the ENSEMBL database at the Sanger Institute. Identified mutations were further validated by comparison against databases such as SNPper and HapMap to confirm their presence and significance.

ELISA for gCD59

Plasma levels of gCD59 were quantitatively determined in all participants through a sandwich ELISA assay (USCN Life Science Inc., Wuhan, China). Initially, 100 µL of each serum sample or standard was applied to microtiter plates pre-coated with the target protein. Subsequently, biotin-conjugated antibodies specific to the protein of interest were added as secondary antibodies for detection. The assay was conducted strictly by the manufacturer's guidelines. Optical density readings were taken at 450 nm, and the concentration of the protein candidates within the samples was calculated by referencing a standard curve.

Statistical analysis

Continuous variables were reported as mean±standard deviation with interquartile range, while categorical variables were expressed as proportions. T-tests were used for continuous variables, and Chi-squared or Fisher's exact tests for categorical variables. The Kruskal–Wallis test, followed by Dunn's post hoc analysis, evaluated median differences across groups. Receiver Operating Characteristic (ROC) curve analysis assessed model predictive accuracy using the area under the curve (AUC), with Z statistics comparing AUCs. Patients were classified according to KDIGO guidelines based on the albumin to creatinine ratio (ACR) as low (<30 mg/g) or high (30–300 mg/g). Statistical analyses were conducted using IBM SPSS (version 22.0). A p-value<0.05 was deemed significant. Predictive model performance was assessed via sensitivity, specificity, positive/negative predictive values, and overall accuracy.

Results

Baseline characteristics of participants

The study involved 320 participants with type 2 diabetes (T2D), equally divided into microalbuminuric (n=160) and normoalbuminuric (n=160) groups. The microalbuminuric group was significantly older (62.49±12.14 years) compared to the normoalbuminuric group (49.30±12.25 years, p<0.001). The duration of diabetes was marginally longer in the microalbuminuric group (10.66±5.02 years) compared to the normoalbuminuric group (3.21±2.01 years); however, this difference was not statistically significant (p=<0.001). A summary of the baseline characteristics is provided in Table 1.

Plasma gCD59 and microalbuminuria status

Figure 1 shows that patients with microalbuminuria exhibited significantly higher plasma glycated CD59 (gCD59) levels, with a mean concentration of 711.27±46.75 pg/mL, compared to 424.06±15.75 pg/mL in the normoalbuminuric group (p<0.001; Table 2, Figure 1A). This

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Table 1: Baseline characteristics of participants in the current study.

Variable	All patients	Range	Microalbuminuric patients (n=160)	Normoalbuminuric patients (n=160)	P-value
Sex (M/F)	169/151		72/88	97/63	
Mean age (years)	54.18±13.73	30–85	62.49±12.14	49.3±12.25	<0.001
Mean age at onset of diabetes (years)	48.6±10.5	28–70	51.7±9.8	46±11.6	<0.001
BMI (kg/m^2)	22.09±4.99	11.6–38.2	22.88±6.06	21.64±4.23	0.23
Serum creatinine (mg/dL)	0.97±0.17	0.6–1.3	0.98±0.16	0.97±0.18	0.61
Creatinine clearance (ml/min/m^2)	80.35±21.81	43–166	75.43±20.57	83.24±22.16	0.08
Duration of diabetes (years)	5.97±4.98	1–20	10.66±5.02	3.21±2.01	<0.001

difference represents a nearly 68% increase in gCD59 levels among individuals with microalbuminuria, emphasizing its strong association with early signs of diabetic nephropathy. Such a significant elevation suggests that plasma gCD59 may reflect the pathophysiological changes associated with kidney damage in diabetes, including heightened oxidative stress and the activation of the complement system. The resultant findings underscore the utility of gCD59 as a non-invasive, reliable biomarker for identifying T2D patients at risk of progressing to nephropathy, enabling earlier diagnosis and potentially guiding more personalized management strategies.

HbA1c and microalbumin levels

The mean HbA1c level (Table 2), a critical indicator of long-term glycemic control, was significantly elevated in the microalbuminuric group (9.18±1.54%) compared to the normoalbuminuric group (8.54±1.22%, p<0.001). This 7.5% relative increase in HbA1c levels highlights the greater degree of hyperglycemia in patients with microalbuminuria, which is known to contribute to kidney damage through the generation of AGE products and increased oxidative stress. Similarly, microalbumin levels (Table 2), a key diagnostic marker for incipient nephropathy, were markedly higher in the microalbuminuric group (175.00±10.59 mg/g) compared to the normoalbuminuric group (10.94± 2.25 mg/g, p<0.001). This represents a more than 15-fold elevation in urinary albumin excretion, indicating a clear distinction in renal impairment between the two groups. Elevated microalbumin levels are reflective of early kidney dysfunction, often linked to damage to the glomerular filtration barrier due to prolonged hyperglycemia and hypertension. The significant differences in both HbA1c and microalbumin levels between these groups reinforce the close interrelationship between poor glycemic control and early renal dysfunction. These findings emphasize the critical need for regular monitoring of HbA1c and microalbumin levels to identify individuals at an elevated risk of developing DN. Early detection enables timely interventions and effective management strategies to slow disease progression and reduce the risk of complications.

Correlation analysis

The duration of diabetes exhibited a strong positive correlation with microalbuminuria (r=0.839, p<0.01), indicating a significant association. In contrast, creatinine clearance showed a weak negative correlation with microalbuminuria (r=−0.158, p=0.08), though this relationship was not statistically significant (Figure 2).

FRMD3 gene polymorphisms and diabetic nephropathy

The GG genotype of the rs1888747 polymorphism in the FRMD3 gene was significantly more prevalent among microalbuminuric patients (51.7%) compared to normoalbuminuric patients (41.2%), with a p-value of 0.037. This genotype exhibited a strong association with DN under the recessive model, as shown in Table 3 and Figure 1B.

Creatinine clearance in patients

A notable disparity in creatinine clearance was identified between patients with microalbuminuric patients

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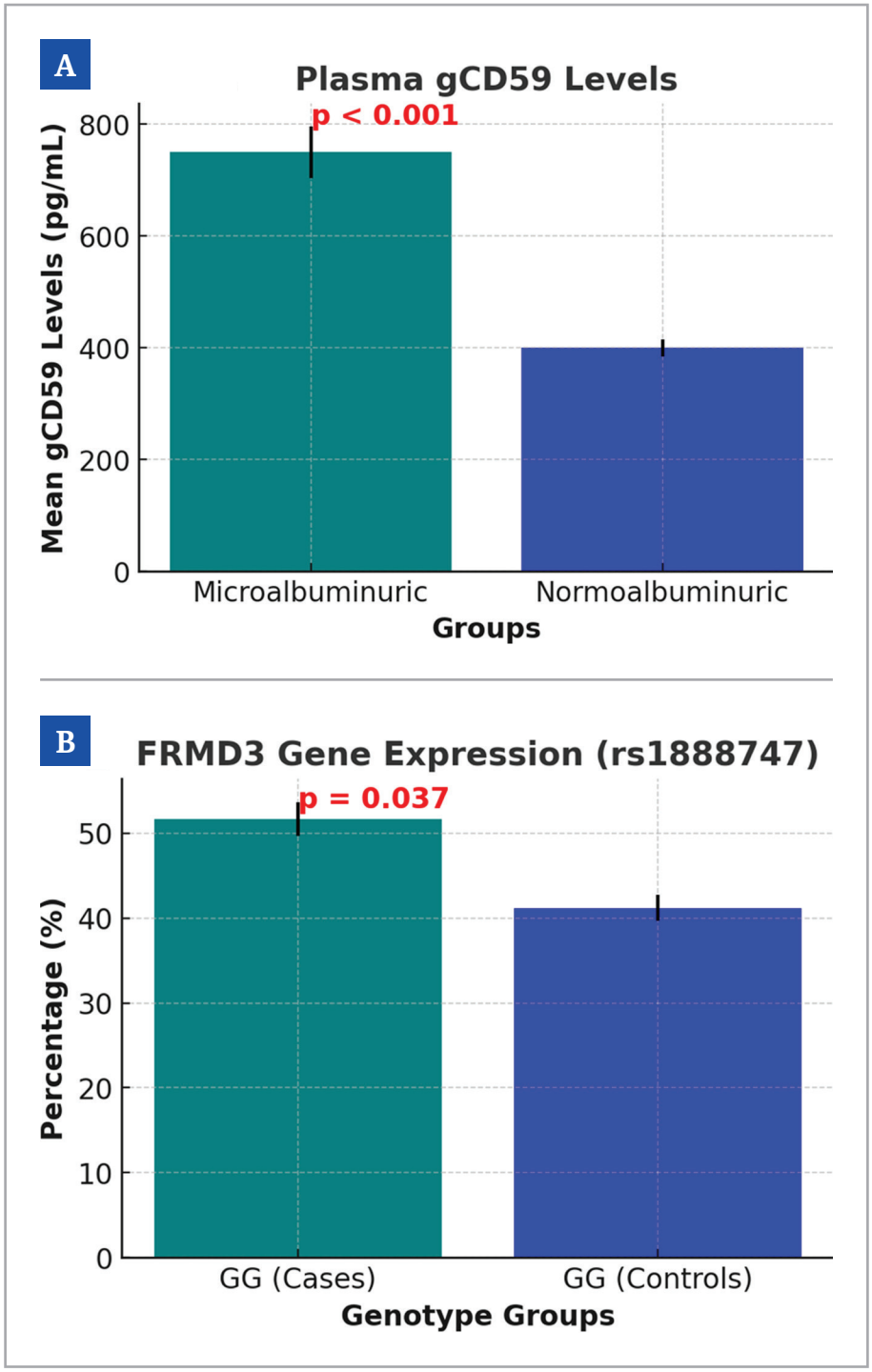

Figure 1: A – Mean plasma gCD59 levels with standard deviations for microalbuminuric and normoalbuminuric groups (p<0.001); B – FRMD3 gene expression (rs1888747 polymorphism) percentages for GG genotype in cases and controls (p=0.037). gCD59 – glycated CD59

Table 2: Comparison of HbA1c, microalbumin, and plasma gCD59 levels in patients.

Variable	Microalbuminuric (Mean±SD)	Normoalbuminuric (Mean±SD)	P-value
HbA1c (%)	9.18±1.54	8.54±1.22	<0.001
Microalbumin (mg/g)	175.00±10.59	10.94±2.25	<0.001
Plasma gCD59 (pg/mL)	711.27±46.75	424.06±15.75	<0.001

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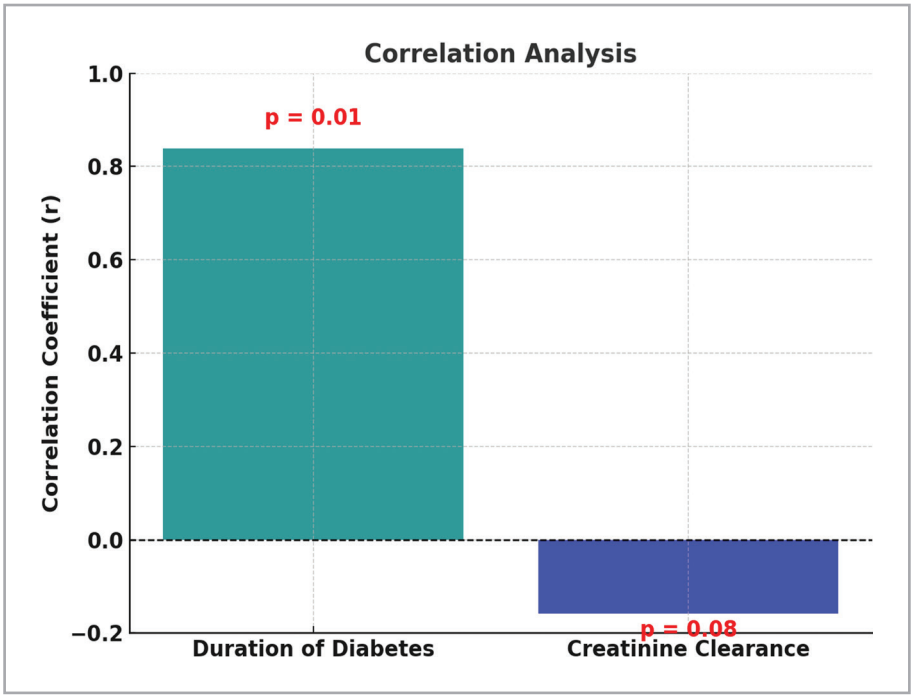

Figure 2: Correlation of microalbuminuria with clinical variables. The teal bar represents a strong positive correlation (r=0.839, p=0.01) between duration of diabetes and microalbuminuria, while the blue bar indicates a weak negative correlation (r=-0.158, p=0.08) between creatinine clearance and microalbuminuria, which is not statistically significant.

(75.43±20.57 ml/min/m^3) compared to the normoalbuminuric patients (83.24±22.16 ml/min/m^3). However, other parameters, such as BMI and serum creatinine levels, did not show any statistically significant differences between patients.

Discussion

Diabetic kidney disease, also known as DN, is a significant complication affecting between 20% and 40% of diabetic individuals [1]. It substantially increases the risk for chronic kidney disease as diabetes prevalence escalates globally, anticipated to impact over 350 million people by 2035 [2]. A cross-sectional study conducted in India examined the prevalence and associations of microalbuminuria in individuals with type 2 diabetes (T2D). The study reported a prevalence rate of around 43.8% [20]. This variation may be attributed to factors like inconsistent treatment adherence and inadequate glycemic control. Inadequate diabetes management, marked by unstable blood sugar levels, is a well-established risk factor for microalbuminuria. Persistent glycemic fluctuations can impair the kidney's filtration mechanism, resulting in albumin leakage into the urine and increasing the risk of DN. This study emphasizes the crucial importance of strict glycemic control in preventing the progression from normoalbuminuria to microalbuminuria, underscoring the vital role of optimal diabetes management in reducing kidney complications in type 2 diabetes (T2D). Maintaining tight glycemic control, combined with targeted interventions addressing modifiable risk factors, is crucial in minimizing the burden of microvascular complications and improving long-term renal outcomes [21, 22].

Interestingly, while confirming a statistically significant correlation between patient age and microalbuminuria, the study found no gender-specific associations or links between BMI and microalbuminuria, contrary to other studies. This discrepancy may be due

Table 3: FRMD3 gene polymorphisms and association with diabetic nephropathy.

Polymorphism	Genotype	Microalbuminuric (%)	Normoalbuminuric (%)	P-value
rs1888747	GG	51.7±2.34	41.2±3.89	0.037
rs9521445	CC	29.2±3.16	27.9±2.05	0.146

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to confounding factors such as diabetes duration and glycemic management, which significantly influence the development of microalbuminuria. No significant associations were found between microalbuminuria and creatinine levels, indicating that it may not directly correlate with abnormal serum creatinine or creatinine clearance. However, microalbuminuria remains a crucial early marker of potential renal damage, emphasizing its role in the early detection and management of DN.

Recent research suggests that a combination of metabolic and hemodynamic factors triggers key intracellular signaling pathways and transcription factors, leading to microvascular damage in the glomeruli and accelerating the progression of diabetic kidney disease (DKD) [23]. Furthermore, the study examined the role of soluble CD59, a variant of the typically membrane-bound protein CD59, which is found in blood, urine, and saliva. Non-enzymatic glycation processes in diabetes can inactivate CD59, resulting in the formation of glycated CD59 [17]. Elevated levels of gCD59, correlated with higher glucose levels, suggest its utility as a potential predictor of nephropathy in T2D patients, as demonstrated through sensitive ELISA assays [24, 25]. The study also investigated genetic predispositions, focusing on the FRMD3 gene, which has been linked to DKD susceptibility through genome-wide association studies (GWAS). This gene encodes structural protein 4.1, which plays a crucial role in maintaining cellular integrity. Notably, polymorphisms in the FRMD3 gene have been associated with varying levels of DKD susceptibility across different populations, underscoring the need for further research to understand these genetic influences better and facilitate the development of targeted therapeutic strategies [19, 26–29].

This study highlights the intricate interplay between genetic and environmental factors in the pathogenesis of DKD, underscoring the need for ongoing research into the underlying mechanisms and risk factors that contribute to this debilitating condition. The findings further underscore the importance of comprehensive clinical assessments, integrated with genetic testing, in improving diagnosis, management, and prognosis. Such an approach can enhance early detection and personalized treatment strategies, ultimately leading to better patient outcomes. Further validation of these findings is required to confirm their clinical utility and establish standardized diagnostic protocols.

The present study validates plasma gCD59 and FRMD3 gene as reliable biomarkers across diverse human cohorts. Furthermore, the mechanism underlying plasma CD59 glycation, as well as the functional role of FRMD3 gene in the kidney, has been evaluated. Looking ahead, the integration of plasma gCD59 as a biomarker, FRMD3 genetic variations, and key clinical characteristics will be essential for improving the prediction and early detection of diabetes in patients.

Conclusions

The study provides compelling evidence supporting the utility of plasma gCD59 and FRMD3 gene polymorphisms as key biomarkers for the early detection and management of DN in patients with T2D. Elevated plasma gCD59 levels were consistently associated with microalbuminuria, reinforcing its role as a reliable early indicator of nephropathy. Additionally, the study identified a significant genetic predisposition to DN, demonstrated by the higher prevalence of the G allele and GG genotype in the FRMD3 gene among affected individuals. The integration of these biomarkers into routine clinical practice could revolutionize the early diagnosis, risk stratification, and personalized management of DN, enabling targeted therapeutic interventions and ultimately improving patient outcomes.

Moving forward, larger-scale, longitudinal studies are crucial to validate these findings further and standardize their clinical application. Establishing these biomarkers in routine screening protocols could lead to significant advancements in the prevention and management of diabetic nephropathy, ultimately helping to reduce its global burden as a major diabetic complication.

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Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The study received institutional ethical committee approval from the Institute of Genetics & Hospital

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for Genetic Diseases, Osmania University, Hyderabad, India (No: 18/EC/NE/INST/2023/4032).

Consent to participate

Written informed consent was obtained from all the participants.

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