Elucidating the Clinical Significance of Serum Free Light Chain Dynamics in Diabetic Kidney Disease

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Abstract: Current conventional markers for diagnosing diabetic nephropathy, such as serum urea, creatinine, and also with serum renalase, often exhibit limited sensitivity and accuracy because significant kidney damage can occur before these biomarkers become elevated. This study aimed to explore the utility of serum free light chains as indicators of disease manifestation in diabetic nephropathy

Methodology: About 60 study participants were selected from the General Medicine OPD from the Tertiary care Hospital based on the age and gender matched depending on the inclusion and exclusion criteria. All the biochemical parameters like Glycemic controls, RFT, LFT, Serum Renalase and Free light chains were analysed by using biochemistry auto analyser and ELISA method.

Statistical Analysis: Data analysis involved descriptive statistics, analysis of variance (ANOVA), Tukey HSD post hoc tests. We employed pearman's correlation to examine relationships between relevant variables. The p value significant at <0.05.Finally, receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of free light chains.

Results: Their average fasting blood glucose (FBG) was 8.0 mmol/L (SD: ±5.86), and the duration of diabetes mellitus (DM) for an average of 11.88 years (SD: ±7.96). Significant correlation of kappa, lambda and kappa:lamda ratio has been observed with other renal markers.

Conclusion: Our current findings indicate an escalating trend in serum free light chain levels with the progression of diabetic nephropathy, though this observation did not reach statistical significance. However, further research is essential to fully establish their predictive utility as a diagnostic tool for this condition.

Key Words

Serum Renalase Serum kappa(K) Serum Labda(L) Serum K/L ratio Type 2 Diabetes Mellitus Diabetic Kidney Disease(DKD) DKD Markers

BACKGROUND

Diabetic nephropathy is the leading cause of end-stage renal disease in developed countries, including the United States. As a microvascular complication, it affects individuals with both type 1 and type 2

diabetes.(1) Significant progress has been made in recent years in understanding the mechanisms of diabetes mellitus, and recent studies have led to updates in treatment guidelines. Staying informed about these latest developments is crucial for providing optimal care to patients with diabetes and kidney disease.(2) The primary pathological features of diabetic kidney disease (DKD) include glomerular hypertrophy, glomerular basement membrane thickening, effacement of podocyte foot processes, and mesangial matrix expansion. Traditional markers of DKD, such as albuminuria and creatinine, are relatively insensitive and have limited utility due to delayed detection. (3)Recent studies have led to updates in treatment guidelines, making it essential to review this extensive topic for providing optimal care to patients with diabetes and kidney disease. Recent guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) and several renal organizations recommend using the terms "diabetes and chronic kidney disease (CKD)" or "diabetic kidney disease (DKD)" instead of "diabetic nephropathy." However, all these terms are currently used in the literature. Additionally, the Kidney Disease Outcomes Quality Initiative (KDOQI) work group emphasizes the need for long-term multidisciplinary teams to address the widespread impact of diabetes and highlights the importance of holistic care and lifestyle modifications for effective management.[4] .Diabetic nephropathy (DN) is a serious and prevalent complication of diabetes, often leading to end-stage renal disease (ESRD). Despite its significant impact, current diagnostic approaches for DN, which primarily rely on conventional markers like serum urea, creatinine, and microalbuminuria, face considerable limitations.(5) These limitations stem from the fact that substantial kidney damage can occur silently, often for years, before these traditional biomarkers become elevated and signal an issue. This delayed detection significantly hinders timely clinical intervention, which is crucial for slowing the progression of the disease and preserving kidney function. Consequently, there is a critical and unmet need for more sensitive and accurate diagnostic tools that can identify DN at much earlier stages, ideally even before irreversible damage has occurred.(6)

A flavoprotein, renalase a FAD-dependent amine oxidase produced in the kidney renal proximal tubules, which penetrates directly the circulatory catecholamines like dopamine, epinephrine, and nor epinephrine (7). Also seen in the heart, skeletal muscles, and small intestine. RNLS is the name of the gene that produces this protein (otherwise called C10 or f59 or FLJ11218). It is likely to be interested in controlling blood pressure function. Renalase has four distinct isoforms (hRenalase1 to hRenalase4), hRenalase1 is primarily found in human blood . The cytoprotective effects hypertension, type 1 diabetes, type 2 diabetes mellitus, obesity, cardiovascular disease, and kidney-related issues are discussed(8)

The Emerging Role of Free Light Chains

Although diabetic nephropathy has been traditionally known to be a non-immune disease, recent studies have shown that immunity and inflammation are vital factors in its development and progression (9). Free light chains are low molecular weight proteins and by-products of immunoglobulin synthesis (10). Free light chains are produced in excess during immunoglobulin synthesis and are cleared from the serum by the kidneys; therefore a decrease in glomerular filtration rate leads to an increase in free light chains. There are two forms of free light chains namely, kappa(k) and lambda(λ) . The serum concentration of free light chains depends on the balance between production and clearance by the kidneys. Free light chains have been shown to have a stronger relationship with renal inflammation than other inflammation markers like CRP (11).

Although microalbumin has been widely employed in the diagnosis of diabetic nephropathy, its sensitivity and accuracy are limited because kidney damage precedes albumin excretion (12). Recent studies have demonstrated that the free light chain is a better marker for the risk of developing kidney damage than other markers of kidney function (13). A study conducted in the United Kingdom demonstrated that serum concentrations of free light chains increased progressively with chronic kidney disease (CKD) stage and also correlated strongly with renal function tests including cystatin C. Another study carried out in the UK among type two diabetes mellitus patients indicate significantly elevated levels of free light chains (FLC) before the development of overt renal impairment, signifying their possible role in predicting early diabetic nephropathy.

In recent years, research has increasingly focused on novel biomarkers that can offer earlier insights into renal health. Among these, serum free light chains (FLCs) have emerged as particularly promising. FLCs are the unbound components of antibodies, produced by plasma cells, and their levels can reflect underlying immune system activation and inflammation.(14) These processes are increasingly recognized as key contributors to the

initiation and progression of DN. By investigating alterations in FLC levels, we might gain a more nuanced understanding of the immune dysregulation that contributes to kidney damage in diabetic patients. In this study we aimed to determine the association between the serum Renalase and the kappa/lambda ratio in the diabetic kidney disease.(15)This study, therefore, aimed to explore the potential of serum FLCs as novel biomarkers for the disease manifestation of diabetic nephropathy. We sought to determine their correlation with established renal markers and serum Renalase evaluate their overall utility in providing earlier insights into kidney damage in individuals with diabetes.

METHODOLOGY

INCLUSION CRITERIA:

T2DM with and without Nephropathy patients with confirmation of urinary dipstick positive for albumin subjects with age of 35-65 years irrespective of gender will be taken from General medicine OPD, followed obtaining written informed consent from the study participants. 4ml of venous blood will be collected under aseptic precautions and medical supervision is collected to analyse fasting blood glucose (FBG), HbA1C, HOMA-IR, Renal Markers, Liver Function Markers, Creat/Albumin ratio and eGFR. Serum Renalase and immunoglobulin free light chains – Kappa, Lamba by ELISA method & Kappa/Lambda ratio was calculated.

EXCLUSION CRITERIA

People with any acute and chronic illness (except T2DM and Nephropathy), gastrointestinal disorders, pregnancy, urinary tract infection and dyslipidemia

Statistical Analysis: Data analysis involved descriptive statistics, analysis of variance (ANOVA), Tukey HSD post hoc tests, and the Kruskal-Wallis test. We employed the Chi-squared test to assess significant associations with our indicators of interest and used Spearman's correlation to examine relationships between relevant variables. Finally, receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of free light chains.

RESULTS

In this study we observed higher levels of serum Free light chains kappa: lambda ratio was associated with increased risk of renal function decline in patients with T2DM and renal dysfunction from the following statistical tools.

Fig 1: Comparison of serum level of Renalase and FLCs K/L ratio

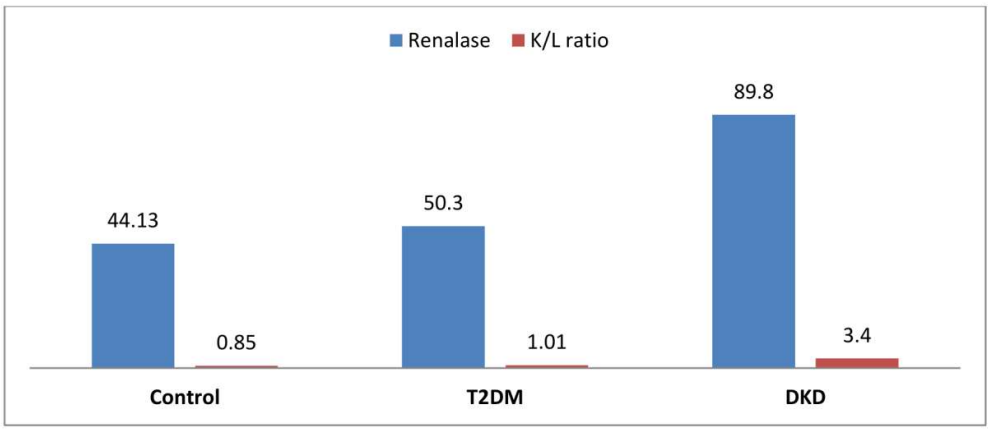


Table 1: Comparison of Mean & SD of different clinical parameters among study groups

Variables	Control(n=60)	T2DM (n=60)	DKD(n=60)
Renalse(ng/ml)	36.133 ±8.059	37.73 ±5.58	48.86 ±11.77
FBS(mg/dl)	95.46± 11.18	177.03±47.68	170.6 ±66.10
HbA1C(%)	4.85 ± 0.49	9.29 ±2.04	8.98 ±1.44
Insulin(ug/ml)	6.3 ±2.0	13.11 ±5.59	13.89±6.23
Creatinine(mgdl)	0.93 ±0.144	0.88± 0.17	5.87 ±2.04
eGFR(mL/min/1.73m2)	98.56 ±24.40	100.83 ±17.78	60.8 ±34.86
HOMA- IR	1.57 ± 0.4	5.741±3.9	5.747 ±3.22
Creat/Alb Ratio	0.225 ± 0.03	0.1991 ± 0.0418	2.97 ± 0.542
L/K ratio	1.01± 0.77	0.898 ± 0.192	6.927 ± 20.34

FBS- Fasting blood glucose, HbA1C – Glycated hemoglobin , eGFR- Estimated glomerular filteration rate, TAG – Triacylglyceride, HDL – High density lipoproteins, Creat- Creatinine, Alb- Albumin

Table 2: Pearson's correlation analysis for T2DM and DKD groups

	Control		T2DM		DKD	
	r value	p value	r value	p value	r value	p value
Insulin	0.1557	0.4113	-0.2112	0.2625	0.1557	0.4113

FBS	0.0021	0.99121	-0.0231	0.9039	0.1178	0.5352
HbA1C	-0.1763	0.3513	0.7698	< .00001	0.239	0.2033
Creatinine	0.1654	0.3824	0.0648	0.7337	-0.6069	0.0003
e GFR	-0.4149	0.2294	-0.1246	0.5138	0.728	< .00001
HOMA IR	-0.0193	0.921	0.454	**0.011**	0.4183	0.0214
Creat/Alb Ratio	0.2145	0.255	-0.4405	**0.0149**	-0.1384	0.4670
L/K ratio	-0.308	0.1666	0.1155	**0.038**	0.2396	**0.0352**

*p value significant at 0.05

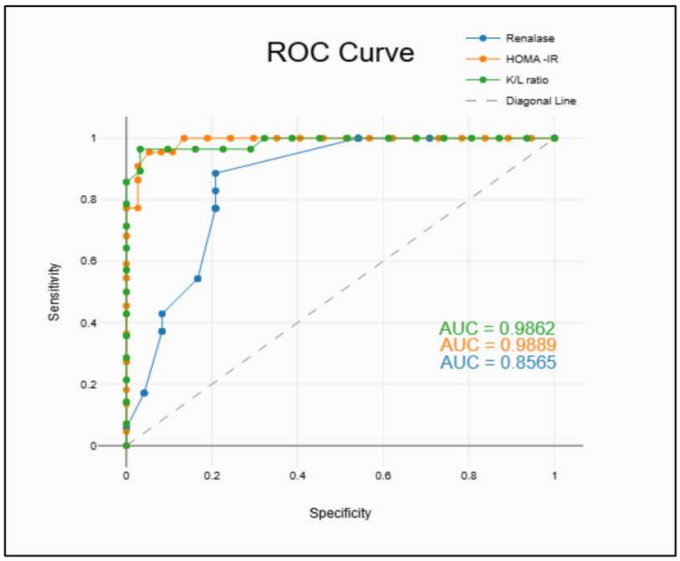
FBS- Fasting blood glucose, HbA1C – Glycated hemoglobin , eGFR- Estimated glomerular filteration rate, TAG – Triacylglyceride, HDL – High density lipoproteins, Creat- Creatinine, Alb- Albumin

Table.3: Comparison of serum K/L ratio among three groups by using ANOVA

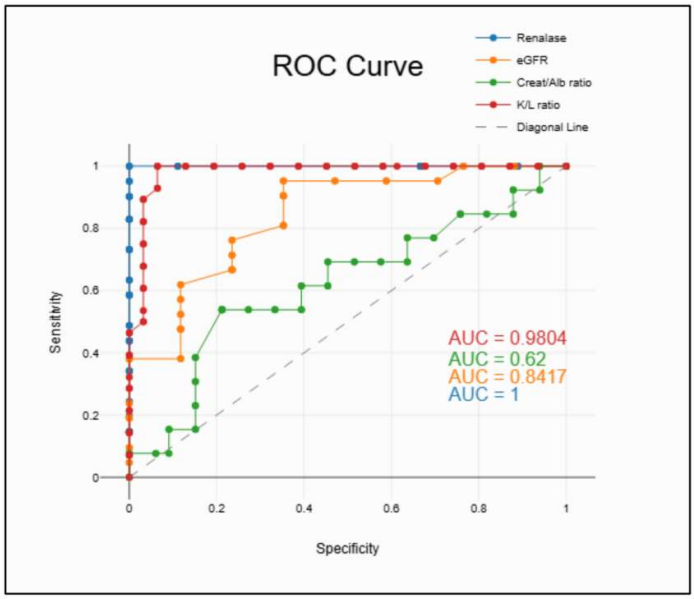
Pairwise Comparisons		$HSD_{.05} = 3.7215$ $HSD_{.01} = 4.6472$	$Q_{.05} = 3.3428$ $Q_{.01} = 4.1743$
T_1:T_2	$M_1 = 36.67$ $M_2 = 3.43$	33.24	Q = 29.85 (p = .00000)
T_1:T_3	$M_1 = 36.67$ $M_3 = 48.20$	11.53	Q = 10.36 (p = .00000)
T_2:T_3	$M_2 = 3.43$ $M_3 = 48.20$	44.77	Q = 40.21 (p = .00000)

T1- Control Group T2- T2DM Group T3 – DKD Group

Fig 2: Receiver operating characteristic curve analysis



(a) Represents the diagnostic value of serum light chain K/L ratio for T2DM patients with area under the curve (AUC) of ROC curve was 0.986 at 95% confidence interval (CI)



(b) Represents the diagnostic value of serum light chain K/L ratio for DKD patients with area under the curve (AUC) of ROC curve was 0.980 at 95% confidence interval (CI)

Discussion

This study investigated the potential of serum free light chains (FLCs), specifically Kappa (κ) and Lambda (λ) and their ratio, as well as renalase, as early indicators of diabetic nephropathy (DN).Our findings, while not reaching statistical significance for all observed correlations, offer promising insights that resonate with and build upon existing literature regarding the limitations of traditional renal markers and the emerging roles of novel biomarkers in kidney disease. The conventional diagnostic paradigm for DN, relying on serum urea,

creatinine, and eGFR is widely acknowledged to have limitations. As highlighted in the introduction, significant kidney damage can silently progress before these markers indicate dysfunction, necessitating the discovery of more sensitive and timely indicators.

Our observation of an increasing trend in serum free light chain levels with the progression of diabetic nephropathy, as there it is statistically significant in this cross-sectional study, aligns with the growing understanding of immune system involvement in DN. FLCs are products of plasma cells and their elevated levels can reflect underlying immune activation and chronic inflammation Nowak & Kyle et.al.,(16) While traditionally associated with monoclonal gammopathies and direct light chain nephropathy, polyclonal FLCs are also known to be elevated in various inflammatory conditions.

A study by Teppo & Groop et.al.(17) though older, is particularly relevant as it noted increased urinary Kappa light chains in diabetic patients, even those without microalbuminuria, suggesting FLCs could be an earlier sign of diabetic nephropathy. More recently, Li et al.(18) suggested that FLC λ and κ/λ ratios might be more specific and sensitive markers for diabetes diagnosis relative to HbA1c, indicating a broader role for FLCs in diabetes-related inflammatory processes, Li et al.,(18). Furthermore, studies have shown that elevated polyclonal FLCs are associated with increased mortality and cardiovascular events in patients with diabetes, reinforcing their potential as general prognostic indicators Mankia et al., (19)

Our findings of a positive, albeit non-significant, correlation between albuminuria and both Kappa and Lambda FLCs are consistent with the idea that immune activation, reflected by FLCs, may contribute to glomerular damage and increased albumin excretion. The lack of statistical significance might be attributed to the cross-sectional nature of our study, where a single measurement may not capture the dynamic interplay of these biomarkers over time, or the diverse stages of DN among our participants. Longitudinal studies, like those suggested by Mankia et al.(20) for cardiovascular risk, would be crucial to determine if FLC elevation precedes or tracks the development of microalbuminuria and overt proteinuria in DN.

The negative, non-significant correlation between albuminuria and the Kappa:Lambda ratio is intriguing. While the ratio is often used to detect monoclonal gammopathies, disturbances in the polyclonal ratio could still reflect a subtle imbalance in B-cell activity or FLC clearance that warrants further investigation. For instance, Vermeersch et al**. (21)** showed that while FLCs increase with declining renal function, the ratio tends to remain stable until very advanced stages of CKD, unless a monoclonal process is present. Our non-significant finding might suggest that in early to moderate DN, the specific disproportionality in FLC production or clearance is not yet distinct enough to manifest a significant shift in the ratio, or that other factors are more dominant.

Diabetic kidney disease (DKD) is a significant microvascular complication of diabetes, characterized by progressive decline in renal function. Our study investigated the relationship between serum renalase levels and markers of B-cell dyscrasia, namely serum free light chains (sFLC) kappa, lambda, and their ratio (kappa/lambda ratio), in patients with DKD.

The findings demonstrate a statistically significant positive correlation between serum renalase levels and the kappa/lambda ratio ($r=0.2396$, $p<0.001$) in patients with diabetic kidney disease. These positive correlations suggest that as serum renalase levels increase, there is a concomitant elevation in the levels of both kappa and lambda free light chains, as well as their ratio.

This observed positive correlation is particularly intriguing given the known roles of both renalase and free light chains in physiological and pathophysiological processes. Renalase, primarily secreted by the kidneys, plays a crucial role in regulating blood pressure and has been implicated in metabolic homeostasis and inflammation. Its levels are often altered in kidney diseases. Previous studies on serum renalase levels in chronic kidney disease (CKD), including DKD, have shown conflicting results. Some studies report elevated serum renalase levels in CKD patients, particularly in those with advanced stages or those with diabetic macroangiopathy, suggesting its potential as an early diagnostic marker for DKD. This elevation could be a compensatory mechanism or a result of reduced renal clearance. Conversely, some older studies indicated decreased plasma levels of renalase in CKD, highlighting the complexity and variability in renalase research Medycyna Praktyczna et. al, (21) Chronic kidney disease is associated with increased levels of renalase in serum and decreased in erythrocytes". Our findings align with studies demonstrating increased renalase in DKD.

On the other hand, sFLCs are components of immunoglobulins, produced in excess by plasma cells. While low levels are normal, elevated sFLCs, particularly an abnormal kappa/lambda ratio, are typically associated with monoclonal gammopathies and B-cell dyscrasias, which can have renal consequences such as light chain cast nephropathy. However, even in the absence of overt monoclonal gammopathy, elevated sFLCs can be observed in various inflammatory conditions and chronic kidney disease (CKD) due to impaired renal clearance or polyclonal B-cell activation. Several studies have shown that sFLC concentrations increase proportionally to the degree of reduction in glomerular filtration rate (GFR) in CKD patients. Furthermore, elevated polyclonal sFLCs are recognized as markers of B-cell inflammatory conditions and have been associated with increased mortality in CKD. There is growing evidence suggesting that sFLCs are better indicators of renal inflammation than other inflammatory markers like CRP, and have shown promise in predicting early diabetic nephropathy.

The positive correlation observed in our DKD cohort could be interpreted through several potential mechanisms, building upon existing literature. Firstly, the progressive decline in renal function characteristic of DKD inevitably leads to reduced renal clearance of both renalase and sFLCs, resulting in their accumulation in the serum. Wang, L., et a.(22). This is a well-established principle for various low-molecular-weight proteins in kidney disease, including sFLCs. If the rate of accumulation is proportional for both renalase and sFLCs, a positive correlation would be expected. However, this purely clearance-driven explanation might not fully account for the observed strength of the correlation, especially given renalase's complex regulation.

Secondly, the inflammatory milieu prevalent in DKD could play a central role. Chronic inflammation is a hallmark of DKD, contributing to its progression. Renalase has been shown to possess anti-inflammatory properties and its levels can be influenced by inflammatory states. Concurrently, chronic inflammation directly stimulates polyclonal B-cell activation, leading to increased production of sFLCs. This has been reported in various inflammatory conditions, and critically, in patients with diabetes and cardiovascular disease, "Elevated serum free light chains predict cardiovascular risk in type 1 diabetes mellitus". Thus, the correlation could reflect a shared inflammatory pathway where both renalase production (perhaps as a compensatory protective response or due to dysregulation) and sFLC production are upregulated as part of the systemic inflammatory response in DKD. Recent reviews highlight sFLCs as novel biomarkers of inflammation in diabetes, emphasizing the critical role of inflammation in diabetes pathogenesis.

Thirdly, a direct or indirect interaction between renalase and B-cell activity or immunoglobulin metabolism cannot be entirely ruled out, though direct evidence specifically linking renalase to B-cells or immunoglobulin synthesis is sparse. Research has shown renalase involvement in metabolic regulation, including in beta-cell stress and metabolism, which indirectly impacts diabetes pathogenesis. While no direct studies link renalase to B-cell proliferation or immunoglobulin synthesis, renalase role in systemic metabolic and cardiovascular regulation suggests potential, yet unexplored, links to broader immune cell function. Elevated renalase might reflect a systemic stress response in DKD that also impacts B-cell behaviour or immune system activation.

Finally, the positive correlation, especially with the kappa/lambda ratio, warrants further investigation into the specific contributions of different FLC types. An elevated ratio, even within the polyclonal range, could hint at subtle shifts in the polyclonal B-cell repertoire or even a subclinical monoclonal gammopathy in the context of DKD, which might be further influenced or reflected by renalase levels. Previous studies have indicated that the kappa/lambda ratio can be a more specific and sensitive marker for the diagnosis of diabetes compared to traditional markers.

In conclusion, the observed positive correlation between serum renalase and sFLCs (kappa, lambda, and their ratio) in DKD patients is a novel finding that integrates with existing literature on renalase role in kidney disease and sFLCs as markers of inflammation and renal impairment. This suggests a potential interconnectedness between renalase metabolism, B-cell activity, and the inflammatory processes in the context of diabetic kidney disease. These findings support the notion that both renalase and sFLCs may serve as valuable biomarkers reflecting disease severity or underlying pathophysiological mechanisms in DKD. Further research is warranted to elucidate the precise mechanisms underlying this observed correlation and to determine its clinical implications, including its potential as a prognostic marker or therapeutic target in DKD. Longitudinal studies and functional experiments are needed to decipher whether renalase directly influences sFLC production or clearance, or if both are independently driven by common inflammatory and metabolic pathways in the complex pathogenesis of DKD.

Limitations and Future Directions

Our study, being cross-sectional, inherently limits our ability to establish causality or the temporal sequence of changes between FLCs, renalase, and the progression of DN. The modest sample size might also have contributed to the lack of statistical significance for some observed trends, particularly for the FLCs' correlation with albuminuria and the FLC ratio. Furthermore, our study did not stratify participants by specific stages of DN or assess the duration of uncontrolled diabetes, which could provide more nuanced insights into biomarker dynamics.

Future research should prioritize prospective, longitudinal studies with larger cohorts. This would allow for tracking FLC and renalase levels over time in diabetic patients, correlating them with the incidence and progression of DN, and establishing their true predictive value. Investigating the specific molecular mechanisms through which FLCs might exert nephrotoxic effects in DN, or how altered renalase levels contribute to disease progression, would be crucial. Furthermore, combining FLCs and renalase with other emerging biomarkers, such as inflammatory cytokines or genetic markers, could lead to a more comprehensive diagnostic panel for early DN detection and risk stratification. The potential for FLCs to serve as a non-invasive tool for monitoring allograft health in the context of antibody-mediated rejection, as alluded to in the initial abstract, also warrants dedicated investigation.

Conclusion

In conclusion, our study, despite its cross-sectional limitations, provides promising evidence for the role of serum free light chains and their ratio, as well as renalase, as potential adjunctive biomarkers in diabetic nephropathy. The observed trends and significant inverse correlation between the κ/λ ratio and renalase contribute to the growing body of literature emphasizing the complex interplay of immune activation and kidney-specific protective factors in DN. Further comprehensive and longitudinal research is indispensable to fully validate their predictive utility and integrate them into clinical practice for earlier diagnosis and improved management of diabetic nephropathy, ultimately leading to better patient outcomes.

Conflict of Interest

Authors declare there is no conflict of interest

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