Research Article

Evaluation of serum soluble CD36 levels in the clinical progression of diabetic nephropathy

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Keywords

Diabetic nephropathy, sCD36, CKD, diabetic complications, renal dysfunction, diagnostic utility, diabetes, novel biomarker

Abstract

Aim: Diabetic nephropathy (DN) is one of the major contributors to end stage kidney disease globally. Reliable biomarkers for early diagnosis of DN still exists as a major challenge. Serum soluble CD36 (sCD36) involved in lipid metabolism and oxidative stress has been identified as a likely biomarker of DN. Herein, we assess the relationship between sCD36 and clinical worsening of DN, to determine its potential diagnostic value.

Material and Methods: A case- control study involving 160 participants, categorized into four groups was conducted i.e., healthy individuals, diabetics with normo-albuminuria, microalbuminuria, and macroalbuminuria (n = 40). Demographic variables and biochemical parameters were compared. The concentrations of sCD36 in serum samples were determined, as well as correlation analysis between sCD36, fasting plasma glucose (FPG), HbA1c, urine albumin creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) were performed. The diagnostic performance of sCD36 was determined using receiver operating characteristic (ROC) curve.
Results: Serum sCD36 levels rose progressively from 9.97 ng/mL in the control group to 12.13 ng/mL in the macroalbuminuria group, $p < 0.001$. Patients with higher sCD36 levels also had higher fasting plasma glucose, HbA1C, and UACR with a lower eGFR. The ROC analysis of sCD36 gave an AUC of 0.908, showing excellent diagnostic capability of the model. The optimal cut-off value of 10.6 ng/mL yielded 87.5 % sensitivity and 80.83% specificity for detecting advanced DN.

Conclusion: Increased serum sCD36 levels correlates directly to DN progression, hence being a promising candidate biomarker for diagnosis and prognosis. The possible direct application of sCD36 into clinical practice might help improve DN management and treatment.

Introduction

With an International Diabetes Federation (IDF) predicted prevalence of 629 million globally by 2040, Diabetes continues to be one of the most rapidly growing metabolic diseases worldwide with high morbidity and mortality. Significant mortality in diabetes includes cardiovascular diseases, diabetic retinopathy and predominantly diabetic nephropathy (DN). The most common cause of chronic kidney disease (CKD) and renal failure remains to be DN worldwide [1].

The pathophysiology of DN appears to be complex and still remains unclear. The existing treatment strategies for DN stalls the disease but does not reverse or stop its progression into end stage renal disease. Chronic hyperglycemic state associated with diabetes initiates the glomerular injury. This is due to mitochondrial overload following excessive glucose oxidation, which results in over production of reactive oxygen species (ROS). The Tubular epithelial cells (TECs) in proximal tubules with their high mitochondrial content, primarily derive energy through mitochondrial fatty acid oxidation (FAO). Studies have reported dysfunction in FAO as a key factor for development of diabetic kidney disease (DKD) [2-4]. Accumulation of ROS and advanced glycation end products (AGE) leads to release of inflammatory cytokines and activation of excessive glomerular extracellular matrix synthesis [5,6]. Early abnormalities in DN affect the glomeruli primarily, followed by its progression to a tubulo-interstitial disease. Beginning with glomerular hyperfiltration, podocyte damage, glomerular hypertrophy, basement membrane thickening, progressing to mesangial expansion and glomerular sclerosis. Alongside glomerular involvement, recent studies show tubular epithelial degeneration, atrophy and tubulointerstitial sclerosis as an important part in progression of DN [5].

Currently DN diagnosis and progression is studied with the use of markers such as albuminuria, estimated glomerular filtration rate (eGFR), Urine albumin creatinine ratio (UACR), cystatin C. Detectable levels of these markers are observed only after significant renal injury, after which it becomes too late to prevent DN progression to ESRD. Owing to these drawbacks, novel biomarkers like CD36 are required in predicting early damages in DN [7].

Cluster of differentiation 36 (CD36) is a heterodimeric single chain transmembrane surface protein that belongs to class B scavenger receptor family. It functions primarily as a long chain fatty acid transporter protein and through a signalling receptor, CD36 also responds to innate immune reactions. CD36 is expressed ubiquitously on several cells such as macrophages, monocytes, enterocytes, hepatocytes and in renal tissues, it is seen on tubular epithelial cells, podocytes, mesangial cells and endothelial cells. Long chain fatty acids, oxidised LDL, AGEs, advanced oxidation protein products (AOPPs), thrombospondin and S100 family proteins are some of the important ligands of CD36 [3,8,9]. CD36 serves as a signalling centre for lipid homeostasis, immune responses and energy availability equilibrium. CD36 expression has been observed to be upregulated in hyperlipidemic and hyperglycemic states especially in renal tissues in DKD. Disturbances in the CD36 dependent pathways has shown to play a pivotal role in development of renal fibrosis and DKD progression [10]. Though a membrane glycoprotein, the levels of the extracellular portion known as soluble CD36 (sCD36) seen in circulation, has been implicated in various disease conditions such as hepatic steatosis, obesity, insulin resistance, atherosclerosis and diabetes [11,12]. In spite of its role in development of DN and other diabetic complications, only a few studies exist that have depicted the role of sCD36 in clinical setting of DN.

This study was aimed to evaluate serum soluble CD36 levels in patients at various stages of DN and its correlation with disease severity markers like urine albumin creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). Thereby assessing whether serum soluble CD36 can be used as an early predictor of the clinical progression of DN.

Methology

This case control study was conducted in the Department of Biochemistry and Department of Nephrology, Sri Ramachandra Institute of Higher Education and Research, Chennai. The study was carried out from July 2023 to April 2024 following approval by Institutional ethics committee. Sample size calculation software (PS version 3.1.6) was used to calculate the sample size. With type I error as 1% and power of the study as 95% sample size was calculated as

Group 1 (controls) – 40 participants

Group 2 (cases) Diabetic with normo-albuminuria- 40 participants

Group 3 (cases) Diabetic with microalbuminuria- 40 participants

Group 4 (cases) Diabetic with macroalbuminuria- 40 participants

The participants of the study were divided into four groups based on the following inclusion criteria in Table 1.

Table 1: Inclusion criteria of study population.

	Group 1 (Controls)	Group 2 (Cases)	Group 3 (Cases)	Group 4 (Cases)
Subjects	Healthy subjects with normal glucose tolerance	Type 2 diabetic patients with normal albuminuria	Type 2 diabetic patients with micro albuminuria	Type 2 diabetic patients with macro albuminuria
Fasting plasma glucose (FPG)*	<110 mg/dL	≥126 mg/dL	≥126 mg/dL	≥126 mg/dL
Post prandial plasma glucose*	<140 mg/dL	≥200 mg/dL	≥200 mg/dL	≥200 mg/dL
HbA1C*	<5.7%	≥6.5%	≥6.5%	≥6.5%
Urine Albumin Creatinine ratio (UACR)	<30 mg/g of creatinine	<30 mg/g of creatinine	30–300 mg/g of creatinine	>300 mg/g of creatinine

*According to WHO diagnostic criteria for Diabetes mellitus

Patients with Type 1 diabetes, kidney disease other than diabetic nephropathy, anemia, cardiovascular disease, liver disease, cancer, hypothyroidism and current history of any known infection or inflammatory diseases were excluded from the study.

The participants were briefed about the study protocol and written informed consent was obtained from all participants fulfilling inclusion criteria. Venous blood samples were collected from the participants for routine investigations were centrifuged at 3000 rpm for 15 min. Demographic data and relevant laboratory data such as fasting plasma glucose (FPG), total cholesterol (TC), high density lipoprotein - cholesterol (HDL-C), low density lipoprotein - cholesterol (LDL-C), urea, creatinine, urine albumin creatinine ratio (UACR). Urine albumin-creatinine ratio were obtained from patient records. Estimated glomerular filtration rate (eGFR) was calculated by CKD EPI -2021 equation based on serum creatinine values using an online calculator.

Laboratory analysis for the above clinical chemistry parameters was done on Roche COBAS c702 automated chemistry analyser & remaining separated serum samples were aliquoted into Eppendorf tubes and stored at –20° C for analysis of serum sCD36. Serum sCD36 was estimated using precoated sandwich-type ELISA kits approved for research use (ELABSCIENCE E-EL-H104). The kit had sensitivity of 0.1 ng/ml, detection range of 0.16 – 10 ng/ml, with highest intra – assay variability of 5.11% and inter – assay variability of 8.26%.

Statistical analysis was performed using R software version 4.0.2. The normality of data was assessed using Kolmogorov – Smirnov test. The results were expressed as mean and standard deviation. One-way ANOVA was used as the test of significance between groups for continuous variables. Post hoc analysis was done using Tukey – HSD test. Correlation between the variables was analysed using Pearson's correlation test. To assess the performance of sCD36 levels in predicting DN, receiver operating characteristic (ROC) curve analysis was applied and the cut-off value was calculated. A p-value <0.05 was considered statistically significant.

Results

The study examined 160 people categorized into four groups: controls, diabetic patients with "normo-albuminuria, microalbuminuria, and macroalbuminuria, with 40 participants in each category". The average age (Table 2) was markedly greater in the macroalbuminuria group (56.77 years) than in the control group (46.90 years), with a p-value of 0.006. No significant gender difference was seen across the groups (p = 0.064).

Table 2: Baseline characteristics of the study participants.

Characteristic	Control n = 40	DM with normo-albuminuria n = 40	DM with microalbuminuria n = 40	DM with macroalbuminuria n = 40	p-value
AGE (years)#	46.90 (15.87)	49.73 (11.97)	55.27 (12.44)	56.77 (14.66)	0.006#
SEX					0.064
Female	15 / 40 (38%)	14 / 40 (35%)	24 / 40 (60%)	14 / 40 (35%)	
Male	25 / 40 (62%)	26 / 40 (65%)	16 / 40 (40%)	26 / 40 (65%)	

#statistically significant difference between groups observed with p value < 0.05

Table 3 illustrates a gradual rise in fasting plasma glucose and HbA1C levels throughout the groups, with glucose levels escalating from 88.42 mg/dL to 162.85 mg/dL and HbA1C rising from 5.44% to 8.84% in the control and macroalbuminuria groups respectively ($p<0.05$). In a similar manner, serum creatinine concentrations reached their peak and eGFR values exhibited a substantial reduction to 66.25 mL/min/1.73 m² in the macroalbuminuria cohort ($p< 0.001$).

Table 3: Comparison of biochemical parameters between the group.

Characteristic (units)	Control n = 40	DM with normo albuminuria n = 40	DM with micro albuminuria n = 40	DM with macro albuminuria n = 40	p-value
Fasting plasma glucose (mg/dL)	88.42 (10.76)	127.45 (42.42) [a]	165.30 (95.37) [a,b]	162.85 (63.86) [a,b]	<0.001*
HbA1C (%)	5.44 (0.23)	7.31 (1.62) [a]	8.89 (2.51) [a,b]	8.84 (2.19) [a,b]	<0.001*
Serum creatinine (mg/dL)	0.85 (0.14)	0.84 (0.25)	0.86 (0.30)	1.76 (1.52) [a,b,c]	<0.001*
Total Cholesterol (mg/dL)	156.88 (17.75)	201.70 (38.85) [a]	185.43 (54.60) [a,b]	210.35 (60.59) [a,b,c]	<0.001*
LDL-C (mg/dL)	92.67 (13.75)	134.40 (27.56) [a]	118.98 (40.53) [a,b]	140.50 (43.41) [a,c]	<0.001*
HDL-C (mg/dL)	50.98 (6.74)	46.62 (10.11)	44.65 (7.91) [a,b]	46.62 (12.48) [c]	0.003#
Triglycerides (mg/dL)	89.83 (28.78)	158.75 (74.07) [a]	175.50 (98.78) [a,b]	186.72 (116.65) [a,b,c]	<0.001*
Urine Microalbumin (µg/mg of creatinine)	6.18 (4.31)	13.22 (9.93) [a]	88.59 (68.68) [a,b]	508.96 (214.97) [a,b,c]	<0.001*
Urine creatinine (mg/dL)	84.38 (53.47)	105.70 (64.70)	100.53 (66.88)	95.30 (64.25)	0.6
Urine albumin creatinine ratio (UACR) (mg/g of creatinine)	11.31 (14.34)	14.01 (7.04) [a]	111.18 (96.51) [a,b]	719.73 (538.00) [a,b,c]	<0.001*
eGFR (ml/min/1.73m²)	103.53 (10.68)	101.67 (18.33)	90.35 (23.02) [a,b]	66.25 (35.47) [a,b,c]	<0.001*
sCD36 (ng/mL)	9.97 (1.33)	10.76 (0.69) [a]	11.77 (0.50) [a,b]	12.13 (1.11) [a,b,c]	<0.001*

(DM: Diabetes Mellitus; LDL-C: Low density lipoprotein – cholesterol, HDL-C: High density lipoprotein – cholesterol, eGFR: estimated glomerular filtration rate); *Statistically significant difference between groups observed with p value < 0.001, # Statistically significant difference between groups observed with p value < 0.05; a = p value < 0.05: comparison with control; b = p value < 0.05: comparison with DM with normoalbuminuria; c = p value < 0.05: comparison with DM with microalbuminuria

The lipid profile analysis among the groups in Table 3 showed an increase in total cholesterol levels, LDL-C in the macroalbuminuria group, but HDL-C had a little decline from 50.98 mg/dL to 46.62 mg/dL. Triglycerides exhibited a substantial rise across groups ($p < 0.001$). UACR significantly escalated from 11.31 mg/g in the control group to 719.73 mg/g in the macroalbuminuria group, with a p-value < 0.001. Levels of sCD36 were markedly increased among the groups, escalating from 9.97 ng/mL in controls to 12.13 ng/mL in the macroalbuminuria group ($p < 0.001$).

Figure 1: Box Whisker plot showing levels of sCD36 among study participants.

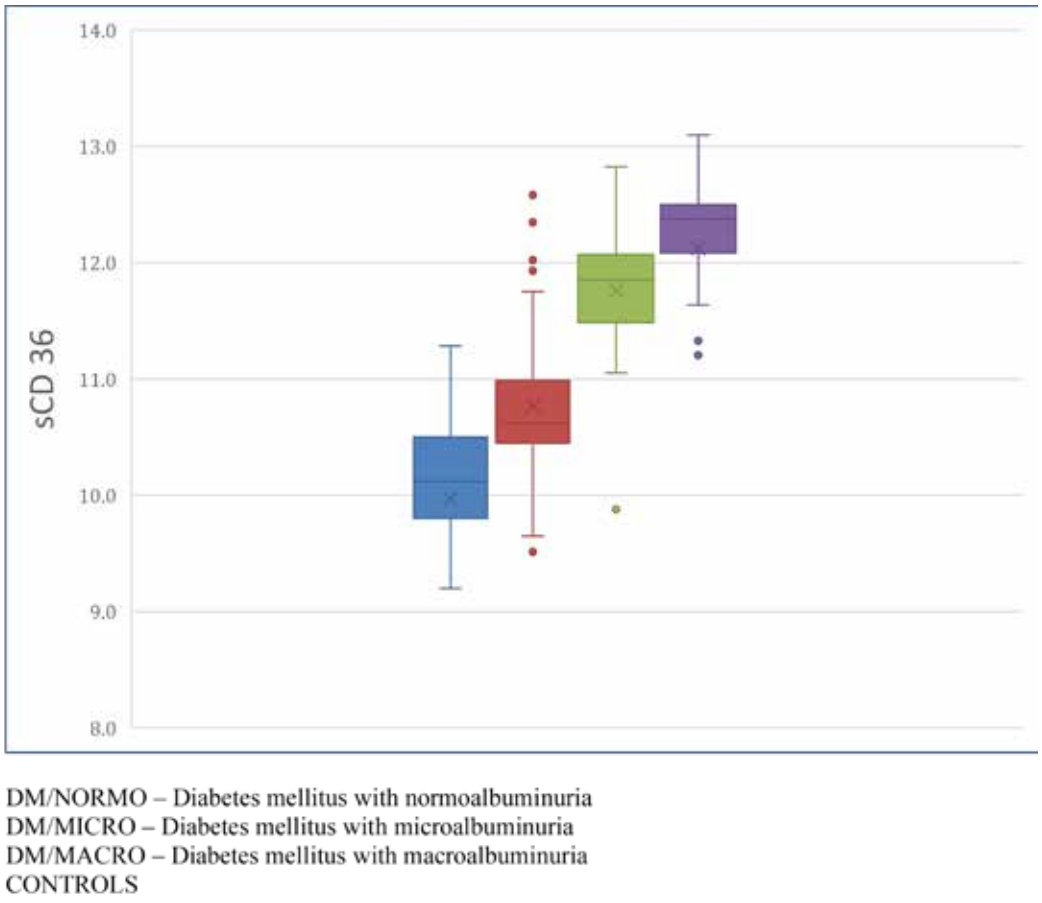


Figure 1 presents a box-whisker plot demonstrating the increase of sCD36 levels according to the severity of diabetic nephropathy.

Table 4 presents correlation analysis, indicating significant associations between sCD36 and fasting glucose ($r = 0.355$, $p < 0.001$), HbA1C ($r = 0.448$, $p < 0.001$), microalbuminuria ($r = 0.429$, $p < 0.001$), and UACR ($r = 0.321$, $p < 0.001$) and eGFR ($r = -0.262$, $p < 0.001$).

Table 4: Correlation between sCD36 and biochemical parameters.

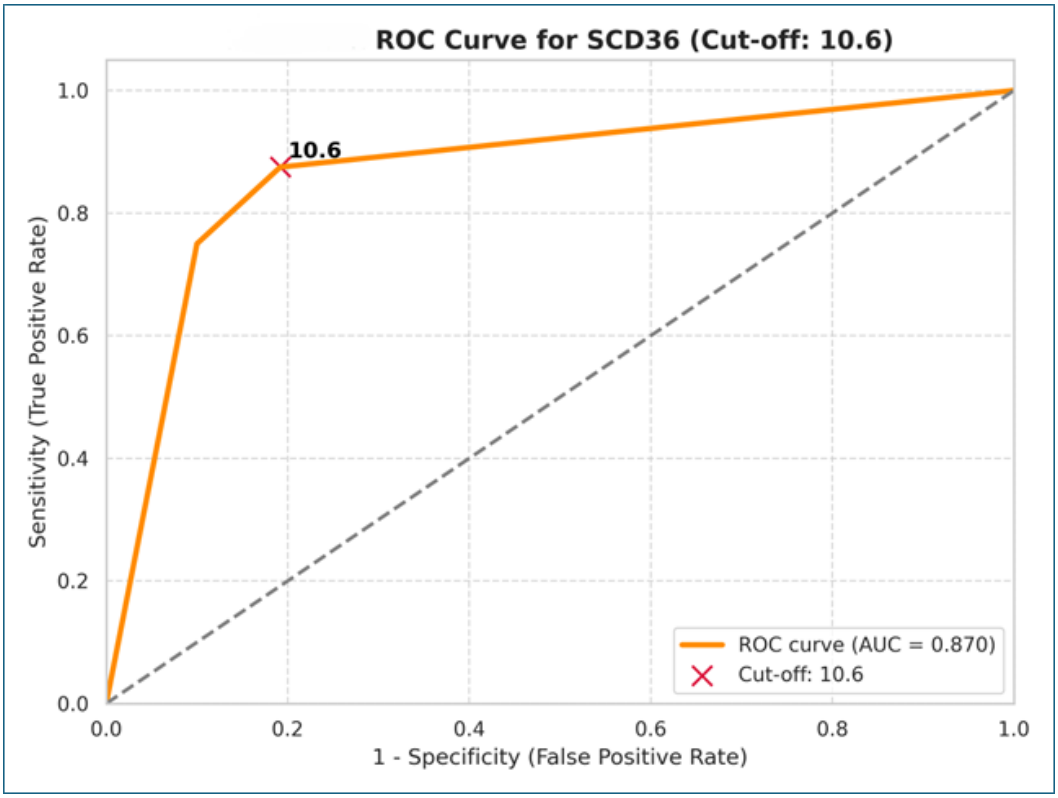
Parameters (units)	sCD36 Correlation Coefficient (r)	p-value
Fasting plasma glucose (mg/dL)	0.355	<0.001*
HbA1C (%)	0.448	<0.001*
Serum Creatinine (mg/dL)	0.085	0.285
Total Cholesterol (mg/dL)	0.168	0.034*
LDL-C (mg/dL)	0.199	0.012*
HDL-C (mg/dL)	-0.073	0.361
Triglycerides (mg/dL)	0.188	0.017*
Microalbuminuria (µg/mg of creatinine)	0.429	<0.001*
Urinary Creatinine	-0.073	0.357
UACR (mg/g of creatinine)	0.321	<0.001*
eGFR	-0.262	<0.001*

(LDL-C: Low density lipoprotein – cholesterol, HDL-C: High density lipoprotein – cholesterol, UACR – Urine albumin creatinine ratio, eGFR: estimated glomerular filtration rate)

*Statistically significant difference with p value < 0.05

The diagnostic efficacy of sCD36 evaluated by ROC analysis (Figure 2), resulted in an area under the curve (AUC) of 0.908, signifying exceptional predictive capability for detecting advanced diabetic nephropathy. The analysis established that a cut-off value of 10.6 ng/mL for sCD36 had a sensitivity of 87.5% and a specificity of 80.83%. These data indicate that sCD36 is a reliable biomarker for differentiating stages of diabetic nephropathy.

Figure 2: Receiver operating characteristic curve (ROC) for sCD36.



The figure shows the ROC curve of sCD36, with a cut off 10.6, AUC of 0.908 at sensitivity of 87.50% and specificity of 80.83%, positive predictive value of 60.34% and negative predictive value of 95.10%.

Discussion

DN is one of the most important microvascular complications of diabetes mellitus, contributing to the development of ESRD with a high prevalence around the world [13]. It is a substantial concern in public health due to the enormous effects and implication on health services and personal well-being of individuals who develop it [14]. Of all blood-based biomarkers, sCD36 has been a target of research attention because of its roles in lipid metabolism, inflammation, and oxyradical damage in DN [6,15,16]. The result of this study emphasizes on the relationship of serum soluble CD36 (sCD36) as an important marker for DN occurrence and progression of the disease.

Higher serum level of sCD36 in this study was associated with increasing levels of UACR and declining eGFR, strengthening the argument that CD36 actively participates in glomerular and tubular damage in progressive DN stages. These results were similar to study by Shiju et al. where levels of sCD36 in both urine and plasma showed a significant increasing trend across their study groups [12].

Hou et al., in their study state that CD36 participates in ROS generation and activation of NLRP3 inflammasome in hyperglycemia states [17]. A study by Shen et al., observed that through ligand induced signalling of toll like receptors results activation of NF-κB/NLRP3 inflammasome this ends in development of kidney fibrosis and renal insufficiency [18]. Of note, this is consistent with our finding of strong positive associations between sCD36, fasting glucose, and HbA1C, affirming the positive feedback loop between diabetes and DN. Chronic hyperglycemia significantly increases CD36 expression which dysregulates FAO by inhibiting AMPK signalling pathway. This leads to decreased OXPHOS, facilitating a metabolic switch to glycolysis for the energy needs thereby producing an imbalance in accumulation/utilisation of fatty acids and mitochondrial ROS (mtROS) generation [13,19,20]. Activation of NLRP3 inflammasome and IL-1, IL-18, IL-1β secretion occurs in a course and dose dependent manner in renal proximal tubules followed by proteinuria. Gnanaguru G et al. in their study depicted that CD36 as an integral regulatory molecule upstream of NLRP3 inflammasome in inflammatory

response [21]. Pyruvate dehydrogenase kinase 4 (PDK4) is a regulatory enzyme for increased utilisation of fatty acids in proximal TECs. In an experimental study by Niu et al., PDK4 upregulation observed in CD36 knockout models indicates that CD36 inactivates PDK4 in DN resulting in changes with AMP activated protein kinase (AMPK) levels. These findings corroborate with our analyses where higher sCD36 levels are significantly negatively associated with eGFR [22-24]. Thus, sCD36 may serve as a biomarker of the more advanced stages of DN in which mitochondrial dysfunction may be common. We have also found positive correlation between sCD36 and dyslipidemia markers including elevated LDL and triglycerides in our study supporting the idea that CD36 might be a useful biomarker for detecting metabolic dysfunction in DN. Su et al., in their study have emphasised the link between CD36 in lipid deposition and renal tubular damage could be due to sodium dependent glucose transporter 2 (SGLT2) together with fatty acid binding protein 4 (FABP4). These parities may imply that sCD36 may be a better biomarker for renal injury and lipid induced renal damage in DN [25].

Notably, the diagnostic performance of sCD36 noted in our ROC analysis with AUC 0.908 is well supported by works of Zhang et al. and Niu et al. that has established relationship between CD36 and renal disease progression in IgA nephropathy and DN respectively. As with other parameters examined in the present study, a correlation between sCD36 and UACR implies that CD36 could also be considered as pathogenic factor in kidney fibrosis and remodelling as elucidated earlier [23,24].

Several studies have demonstrated the possibility of sCD36 as a therapeutic target. Sodium dependent glucose transporter 2 (SGLT-2) inhibitors are a unique class of anti-diabetic drugs that reduce glucotoxicity by increasing sodium dependent glucose excretion in proximal TECs. In a study by Huang et al showed that SGLT-2 inhibitor Empagliflozolin decreased the expression of CD36 at a transcriptional level through PPAR-γ thereby mitigating the downstream activation of inflammatory cascade and stalling progression of DN [25]. In a study by Zou et al, Fisetin, an anti-inflammatory molecule has been shown to inhibit transforming growth factor – β (TGF-β), a cytokine downstream of CD36 involved in mesangial cell hypertrophy and ECM accumulation in renal tissues [26]. These findings underscore the advantage of developing CD36 targeted treatments especially in late stages of DN for which there are few treatment options which needs further validation.

In summary, our study indicates that sCD36 is a useful diagnostic marker and an independent predictor of prognosis in DN. The potential of sCD36 to be a biomarker for identifying the progression of DN is validated in our study by demonstrating its positive relationship with both metabolic and renal parameters, meanwhile exhibiting a good sensitivity and specificity for the diagnosis of DN.

The single centric nature of the study may affect the generalizability of its findings and in elucidating a causal relationship between the marker and DN. Duration of diabetes, medication usage, and lifestyle variables were not studied which may have affected the observed relationships. SCD36 testing in regular clinical examinations for diabetics, particularly those with microalbuminuria, may help to detect and treat DN early. Serum soluble CD36 (sCD36) could be tested in bigger, multi-centre studies with varied populations to demonstrate its diagnostic and prognostic usefulness. The molecular significance of sCD36 in mitochondrial dysfunction and inflammation needs more validation to create targeted therapies. Interdisciplinary research is needed to understand how metabolic control, lipid dysregulation, and CD36 affect DN pathogenesis.

Conclusion

This research underscores the substantial correlation between serum soluble CD36 levels and the clinical progression of diabetic nephropathy. Increased sCD36 levels were shown to correspond with critical markers of diabetic nephropathy severity, including fasting hyperglycemia, HbA1C, urine albumin-creatinine ratio, and decreased eGFR. The diagnostic effectiveness of sCD36 was established by comprehensive ROC analysis, highlighting its potential as a dependable biomarker for the staging and monitoring of diabetic nephropathy (DN). This work identifies sCD36 as a viable biomarker, facilitating its incorporation into clinical practice for early diagnosis and risk stratification of diabetic nephropathy (DN).

Author Contribution

Concept – Iyyama Gowri Moovendhan, Roopa A K, Karthick E, M Ganesh, K Sowmya;
Design - Iyyama Gowri Moovendhan, Roopa A K, Karthick E, M Ganesh, K Sowmya;
Supervision - Iyyama Gowri Moovendhan, Roopa A K, Karthick E, M Ganesh, K Sowmya;
Data collection and processing - Iyyama Gowri Moovendhan, Roopa A K, Karthick E, M Ganesh, K Sowmya;
Analyses and interpretation - Iyyama Gowri Moovendhan, Roopa A K, Karthick E, M Ganesh, K Sowmya;
Literature search - Iyyama Gowri Moovendhan, Roopa A K, Karthick E, M Ganesh, K Sowmya;
Writing - Iyyama Gowri Moovendhan, Roopa A K, Karthick E, M Ganesh, K Sowmya;
Critical review - Iyyama Gowri Moovendhan, Roopa A K, Karthick E, M Ganesh, K Sowmya

Ethical Committee Approval

The study was approved by Sri Ramachandra Institute of Higher Education and Research Institutional Ethics Committee (REF: IEC-NI/23/AUG/88/48).

Data Availability

The datasets used and or analysed during the current study are not available because of institutional policy

Conflict of Interest

The authors declare that there are no conflicts of interest pertaining to conduct of this study.

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