ORIGINAL ARTICLE

AL-ANBAR MEDICAL JOURNAL
Anb. Med. J. 21(2): 117–122, 2025

Evaluation of SH3YL1 Protein as a Potential Biomarker in Different Stages of Diabetic Nephropathy

Rand Jalal Abd Al-Ghanny,[1] Noor Ulhuda G. Mohammed,[2,*] Refif Sabih Al Shawk,[3] Samara Ali Mutar,[2] Hussein Hatam Omran,[4] and Ahmed R. Oleiwi[5]

[1] *Directorate of Research and Development, Ministry of Higher Education and Scientific Research, Baghdad, Iraq.*
[2] *Department of Chemistry, College of Science for Women, University of Baghdad, Baghdad, Iraq.*
[3] *Microbiology Department, College of Medicine, Mustansiriyah University, Baghdad, Iraq.*
[4] *Department of Internal Medicine, Marjan Teaching Hospital, Babil Health Directorate, Babil, Iraq.*
[5] *Department of Laboratories, Mahmoudia General Hospital, Al-Karkh Health Directorate, Baghdad, Iraq.*
(Received : 1 November 2024; Accepted : 6 February 2025; First published online: 26 March 2025)

ABSTRACT

Background: Diabetic nephropathy (DN) is the most prevalent complication of diabetes. Timely diagnosis of DN is important to prevent long-term renal damage and to assess the prognosis of DN patients.
Objectives: To investigate the levels of newly circulating Src homology 3 (SH3) domain-containing Ysc84-like 1 protein (SH3YL1) in various stages of DN among type 2 diabetes mellitus (T2DM) patients and to determine the relationship between SH3YL1 levels and DN by comparing them with traditional diagnostic biomarkers.
Materials and methods: This case-control study included 108 participants, comprising 81 patients with T2DM divided into three subgroups based on the albumin creatinine ratio (ACR): G1 only (27 T2DM with normoalbuminuria), G2 (27 T2DM with microalbuminuria), and G3 (27 T2DM with macroalbuminuria) compared with G4 [27 healthy subjects' group (HS)]. All participants underwent a comprehensive history, examination, routine laboratory analysis, and SH3YL1 measurement via enzyme-linked immune sorbent assay. Furthermore, the ROC curve comparison of SH3YL1 with traditional biomarkers was conducted using the DeLong's test.
Results: A significant increase in serum SH3YL1 levels was shown in G2 and G3 compared to the G4 group. SH3YL1 levels were positively correlated with blood urea and creatinine, while they were negatively correlated with estimated glomerular filtration rate (eGFR) (P-value < 0.0001). Additionally, in multivariate regression analysis, SH3YL1 was found to be significantly independent of blood urea and eGFR (P-value < 0.05). The receiver operating characteristic curve analysis indicated that SH3YL1 effectively discriminates T2DM and DN patients from HS, with an area under the curve of 0.98 and a cut-off value of > 1.1.
Conclusion: SH3YL1 protein may serve as a biomarker for T2DM with different stages of DN, particularly in cases of macroalbuminuria, potentially aiding in early detection and treatment. SH3YL1 and routine biomarkers of DN patients may enhance and improve the diagnostic ability.
Keywords: Albumin creatinine ratio; Diabetic nephropathy; estimated glomerular filtration rate; SH3YL1; Type 2 diabetes mellitus.

DOI: 10.33091/amj.2025.154918.1982

INTRODUCTION

Diabetic nephropathy (DN), is the leading cause of end-stage kidney disease, characterised by albumin excretion and a gradual decline in the glomerular filtration rate [1, 2]. Albuminuria is commonly used to indicate the early stages of DN though it

* Corresponding author:E-mail:noorulhuda.g@csw.uobaghdad.edu.iq

is limited by the fact that structural damage may precede albumin excretion [3, 4]. The accuracy and specificity of these indicators are not optimal, with around 20–30% of patients with DN exhibiting renal failure without albuminuria [5, 6]. Moreover, the albumin creatinine ratio (ACR) is considered a standard diagnostic and prognostic marker for DN, but when ACR is less than 300 mg/24 hours, its sensitivity for DN is reduced [7]. Consequently, it cannot be entirely relied upon for diagnosing and monitoring the progression of diabetic renal disease. Studies have also indicated that microalbuminuria may progress in patients with chronic kidney disease without diabetes [8, 9]. Therefore, there is a pressing need for early diagnostic biomarkers to predict and monitor the various stages of DN.

One promising biomarker is the Src homology 3 (SH3) domain-containing Ysc84-like 1 (SH3YL1), which has been reported to regulate nicotinamide adenine dinucleotide phosphate oxidases (NOX4) [10]. The development of DN is influenced by numerous factors, with oxidative stress closely associated with renal inflammation and fibrosis. The action of NOXs plays a critical role in generating reactive oxygen species (ROS) [11]. NOX4 is one of the seven NOX isoforms [12]. A recent study demonstrated that SH3YL1 protein is synthesised by kidney cells, including mesangial cells, podocytes, and proximal tubular cells, in response to glucose stimulation, implicating it in oxidative stress-induced inflammation [13]. Additionally, another study indicated that SH3YL1 expression was elevated in patients with DN [14]. These findings suggest a significant role for SH3YL1 in DN. It is also essential to recognise that various metabolic, molecular, and hemodynamic factors influence DN. Given the scarcity of clinical studies on this biomarker and its role in kidney injury, hence the study was conducted to analyse the prognostic value of serum SH3YL1 across different stages of DN and determine the relationship between SH3YL1 levels and DN by comparing them with traditional diagnostic biomarkers.

MATERIALS AND METHODS

Study design

This case-control, single-centre study was conducted among DN patients. Patients with T2DM aged between 40–60 years, with a diabetes duration of approximately 8 to 15 years, and a BMI less than 33 Kg/m^2 were recruited from the National Diabetes Centre according to the American Diabetes Association criteria [15], from February to May 2024.

Participants in the study

A total of 108 participants, comprising 81 patients with T2DM who visited the centre for renal injury assessment were enrolled in this study along with 27 healthy subjects (HS). Patients were divided into three groups based on albuminuria, determined by the ACR: G1 (27 patients with normal albuminuria, ACR $<$ 30 mg/g), G2 (27 patients with microalbuminuria, ACR = 30–300 mg/g), and G3 (27 patients with macroalbuminuria, ACR $>$ 300). Additionally, G4 included 27 HS who came to the center included their relatives and had no history of previous diseases were also enrolled in this study. All vital clinical signs of diabetes and DN, such as HbA1c, fasting blood glucose (FBS), and renal function test were measured in HS.

Exclusion criteria included pregnancy, current smoking, active infection, diabetic ketoacidosis, hyperglycaemia, pressure syndrome, congestive heart failure, liver dysfunction, and other causes of renal injury. The participants who declined to participate were also excluded.

Demographic (age and sex) and clinical (such as history of T2DM and its duration) characteristics from each participant were obtained.

Sample collection

Venous blood samples were collected after overnight fasting from participants and divided into two aliquots: The first was placed in an EDTA tube for HbA1c analysis, while the second was placed in a gel tube and allowed to clot at room temperature to obtain serum for measuring (FBG) fasting blood glucose (Reference range 70–110 mg/dl), (BU) blood urea (Reference range 20–45 mg/dl), (SC) serum creatinine (Reference range 0.3–1 mg/dl), lipid profile: (TG) triglyceride (Reference range 60–160 mg/dl), (TC) total cholesterol (Reference range 150–200 mg/dl), (HDL) high-density lipoprotein (35–55 mg/dl), (LDL) low-density lipoprotein (Reference range 0–130 mg/dl), (VLDL) very low-density lipoprotein (Reference range 0–32 mg/dl), and SH3YL1 protein.

Biomarkers and metabolic analysis

All parameters were analysed at the National Diabetes Centre using Cobas C111 instruments. VLDL was calculated using the formula (VLDL = TG/2.2), while LDL-C was calculated using the Friedewald formula. The estimated glomerular filtration rate (eGFR) was calculated using the simplified modification of diet in renal disease [16]. ACR was assessed by dividing the value of urine microalbumin by urine creatinine [17]. SH3YL1 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Mybiosource, USA) according to the manufacturer's instructions.

Anthropometries measurements

Weight and height were measured. The body mass index (BMI) was calculated by formula (weight divided by the square of height) [18].

Ethical consideration

The study complies with the Helsinki Declaration and was approved by the local ethics committee of the National Diabetes Centre (October 20, 2023, Reference number: NDSEC/15/345). All participants provided informed consent.

Calculation of sample size

The sample size was calculated using two mean formulae [19]. It was 28 for each group, in equal sample size of (1:1) with 80% statistical power of 5% level significance.

Statistical analysis

Statistical analyses were performed using the statistical package for social sciences (SPSS), version 25 (IBM company, New York, USA) and MedCalc (version 20.027). The Kolmogorov-Smirnov test was employed to check the normality of variables. Data were expressed for continuous variables as median with interquartile range (IQR) or mean with standard deviation (SD) when skewed and normally distributed, respectively. Differences between study groups were assessed using one-way ANOVA or the Kruskal-Wallis test for normal and skewed variables. Correlation analyses were conducted

http://doi.org/10.33091/amj.2025.154918.1982

Table 1. Baseline demographic, clinical, and laboratory characteristics of the study groups.*

Parameters	G1 (n=27)	G2 (n=27)	G3 (n=27)	G4 (n=27)	P-value
Age (years)	55.33 ± 5.82	52.96 ± 7.51	53.37 ± 5.63	52.59 ± 8.51	0.481
Sex [number (%)]					
Male	8 (29.6)	11 (40.7)	13 (48.1)	8 (29.6)	0.414
Female	19 (70.4)	16 (59.3)	14 (51.9)	19 (70.4)	
Duration	4.11 ± 1.25	8.70 ± 3.10	12.78 ± 0.97	–	0.0001**
BMI (Kg/m^2)	30.09 ± 7.16	28.87 ± 4.37	30.62 ± 4.27	23.39 ± 2.69	0.0001**
Glycaemic marker					
FBG (mg/dl)	180 (144–201)	181 (151–211)	194 (147–293)	104.98 (98.06–109.29)	0.0001**
HbA1C	7.40 (6.9–8.3)	8.90 (7.2–9.9)	8.70 (7.9–9.5)	5.20 (5.4–5.05)	0.0001**
Renal function test					
BU (mg/dl)	19 (17–21)	43 (34–49)	71 (58–85)	16.90 (19.4–13.75)	0.0001**
SC (mg/dl)	0.74(67–91)	1.50(1.4–1.6)	1.90(1.8–2.3)	0.70(0.75–0.5)	0.0001**
ACR (mg/g)	18.90(12.6–18.9)	94.70(94.7–189.4)	493.80(493.8–925.9)	–	0.0001**
eGFR ($ml/min/1.73m^2$)	94.17(88.05–96.93)	45.26(42.88–0.95)	25.22(20.68–29.79)	106.24(111.83–103.3)	0.0001**
Lipid test					
TC (mg/dl)	167 (159–180)	169 (158–187)	183 (169–209)	130 (144–117.5)	0.0001**
TGs (mg/dl)	174 (154–185)	169 (164–184)	187 (165–215)	91 (112.1–86.45)	0.0001**
HDL (mg/dl)	43 (34–46)	41 (35–44)	37 (30–42)	55 (60–52.5)	0.0001**
LDL (mg/dl)	86 (59–103)	84 (70–100)	107 (76–125)	59 (61.5–49.5)	0.0001**
VLDL (mg/dl)	39 (34–43)	40 (36–46)	38 (33–50)	23.60 (26.29–17.1)	0.0001**

* Data are presented as (mean ± SD) or median (IQR).
Comparisons were performed using one-way ANOVA or the Kruskal-Wallis test.
** P-value <0.001 is high significant.
G1: T2DM only patients, G2: Microalbuminuria, G3: Macroalbuminuria ,G4: HS.
BMI: Body Mass Index. FBG: Fasting blood glucose. HbA1C: Glycosylated haemoglobin, BU: Blood urea, SC: Serum creatinine, ACR: Albumin creatinine ratio, eGFR: Estimated glomerular filtration rate, TC: Total cholesterol, TGs: Total glycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very density lipoprotein.

Table 2. S.SH3YL1 levels in study groups.*

Protein Biomarker	G1 (n=27)	G2 (n=27)	G3 (n=27)	HS (n=27)	P-value
SH3YL1(ng/ml)	1.80 (1.63–1.94)[a]	4.13(3.52–4.37)[a,b]	4.64 (4.33–4.91)[a,b]	0.88 (0.98–0.64)	0.0001**

* Data are presented as median (IQR).
Comparisons were performed using the Kruskal-Wallis test and Mann-Whitney test.
** P-value <0.001 is high significant.
G1: T2DM only patients, G2: Microalbuminuria, G3: Macroalbuminuria, G4: Healthy subjects.
a indicates difference between the healthy subjects and patients' groups.
b indicates difference between the type 2 diabetes mellitus and nephropathy groups.

using Spearman's correlation coefficient for continuous variables. Multivariate linear regression analysis was performed to identify independent relationships. To determine the prognostic ability of SH3YL1, receiver operating characteristic curves (ROC) were plotted, and the cut-off value was determined based on the Youden index. The effect sample size was 0.886 at a P-value of < 0.0001, indicating that the dependent variable SH3YL1 has a high chance of detecting the true difference between T2DM and stage 2 diabetic kidney disease.

RESULTS

The mean age and sex showed no significant difference among the four groups. However, patients with DN were significantly older with a longer duration of diabetes than non-DN patients. Additionally, BMI was significantly different among the four groups (P-value = 0.0001). Comparison of glycaemic markers among the studied groups revealed a significant increase (P-value=0.0001). Blood urea (BU), creatinine, and ACR were highest in the G3 group, while eGFR was lowest in the G2 compared to the HS group. Renal function tests showed statistically significant differences between groups (P-value=0.0001). The lipid profiles were highest in the patient groups compared to HS, except HDL was lowest in patients compared to HS, with statistical significance (P-value=0.0001) as shown in Table 1.

Serum SH3YL1 levels were significantly higher in patients' groups compared to HS (P-value = 0.0001). SH3YL1 levels were highest in the G2 and G3 groups compared to G1 and HS (P-value = 0.0001). The differences were statistically significant (P-value=0.0001) among the groups (Table 2).

Table 3. Univariate correlations of the variable with serum SH3YL1 in patients' groups.[†]

Variables		G1	G2	G3
BU	R	0.604 **	0.492 **	0.591 **
	p	(0.001)	(0.009)	(0.001)
SC	R	0.579 **	0.545 **	0.252
	p	(0.002)	(0.003)	(0.204)
LDL	R	0.078	– 0.066	0.387 *
	p	(0.698)	(0.743)	(0.046)
ACR (mg/g)	R	– 0.504 **	0.552 **	0.134 *
	p	(0.007)	(0.003)	(0.025)
eGFR (ml/min/1.73m^2)	R	– 0.55 **	– 0.558 **	0.539 **
	p	(0.003)	(0.003)	(0.004)

[†] R: Correlation Coefficient.
*P-value < 0.05 is a significant correlation.
**P-value < 0.001 is high significant Correlation.
Units of FBG, renal function tests, and lipid profile represented as (mg/dl).
G1: T2DM only patients, G2: Type 2 diabetes mellitus with microalbuminuria, G3: Type 2 diabetes mellitus with macroalbuminuria
BU: Blood urea, SC: Serum creatinine, ACR: Albumin creatinine ratio, eGFR: Estimated glomerular filtration rate, LDL: Low-density lipoprotein.

Table 4. Multivariate linear regression analysis of the relation of SH3YL1 to clinical and laboratory variables.[†]

Variables	Unstandardized Coefficients		Standardized Coefficients	T	P-value
	B	Std. Error	Beta		
Age (years)	-0.004	0.007	-0.017	-0.563	0.575
Sex	-.098	0.097	-0.030	-1.015	0.313
BMI (Kg/m^2)	0.007	0.010	0.026	0.732	0.466
FBG	0.000	0.001	-0.015	-0.385	0.701
HbA1C	0.037	0.039	0.044	0.968	0.336
BU	0.011	0.005	0.169	2.292	0.024*
SC	0.258	0.145	0.114	1.776	0.079
TC	0.001	0.002	0.032	0.779	0.438
TGs	0.001	0.002	0.041	0.920	0.360
HDL	-0.008	0.006	-0.051	-1.250	0.215
LDL	-0.001	0.002	-0.020	-0.501	0.618
VLDL	0.007	0.006	0.047	1.130	0.261
ACR (mg/g)	-0.001	0.000	-0.098	-1.767	0.080
eGFR (ml/min/1.73m^2)	-0.031	0.004	-0.655	-8.359	0.0001**

[†] Units of FBG, renal function test, and lipid profiles are represented as mg/dl.
B: Unstandardised Beta Coefficients.
BMI: Body Mass Index. FBG: Fasting blood glucose. HbA1C: Glycosylated hemoglobin, BU: Blood urea, SC: Serum creatinine, ACR: Albumin creatinine ratio, eGFR: Estimated glomerular filtration rate, TC: Total cholesterol, TGs: Total glycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein.

Serum SH3YL1 levels in all patients' groups were positively and significantly correlated with BU and SC. Conversely, SH3YL1was significantly and negatively correlated with ACR and eGFR. In the G3 group, SH3YL1 was positively and significantly correlated with LDL (Table 3).

Multiple linear regression analysis was conducted to verify independent relationships. eGFR and BU emerged as independent and significant predictors of SH3YL1protein (Table 4).

To assess the discriminative ability of SH3YL1 as a predictor of DN, ROC curves were plotted. SH3YL1 demonstrated excellent discriminates between T2DM and DN, with an AUC of 0.998 (P-value < 0.0001) and cut-off points of >1.1 (ng/ml) at 0.975 (97.53% sensitivity, 100% specificity) as shown in Table 5 and Figure 1A.

Table 6 and Figure 1B show a correlated ROC curve using the DeLong's test to determine the discernment power of each biomarker. There was no significant difference between SH3YL1 and routine analysis of DN patients.

DISCUSSION

The rapid advancement of proteomics technology has supported new methods and insights for recognizing early diag-

http://doi.org/10.33091/amj.2025.154918.1982

Table 5. Area under the ROC curve. Accuracy and cut-off of SH3YL1 in the differentiation between type 2 diabetes mellitus from diabetic nephropathy

AUC	0.988
95% Confidence Interval	0.945 to 0.999
P-value	< 0.0001
Youden Index	0.9753
Associated Criterion (Cut-off)	> 1.1
Sensitivity	97.53
Specificity	100.00
Positive Predictive Value	100.0
Negative Predictive Value	93.1

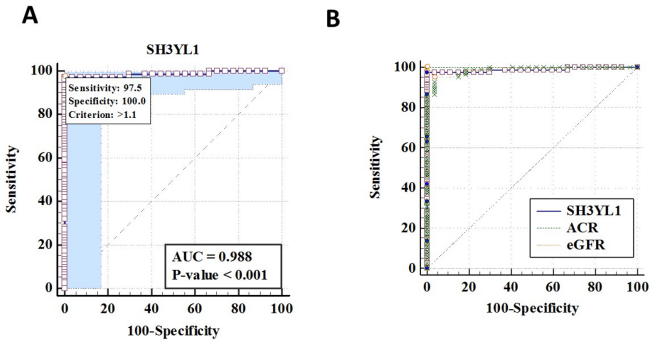

Figure 1. A. Receiving operating characteristic curve of the S.SH3YL1 as a predictor for the diabetic nephropathy (DN) patients. B. Comparing the ROC curve between S.SH3YL1 and routine analysis of DN patients. AUC: Area under the curve, SH3YL1: Src homology 3 (SH3) domain-containing Ysc84-like 1, ACR: Albumin creatinine ratio, eGFR: Estimated Glomerular filtration rate.

Table 6. The comparison between S.SH3YL1 and routine analysis of diabetic nephropathy patients using the DeLong's test for correlated ROC curve*.

Difference Between Areas	SE	95% CI	z Statistic	P-value
ACR ~ eGFR 0.0133	0.00770	– 0.00184– 0.0284	1.721	0.0852
ACR ~ SH3YL1 0.0119	0.00917	– 0.00608– 0.0299	1.297	0.1947
eGFR ~ SH3YL1 0.00137	0.00849	– 0.0153– 0.0180	0.162	0.8716

* SH3YL1: Src homology 3 (SH3) domain-containing Ysc84-like 1, ACR: Albumin creatinine ratio, eGFR: Estimated Glomerular filtration rate, SE: Standard error, CI: Confidence interval.

nostic biomarkers of DN in recent years. The current study found that serum SH3YL1 levels were significantly elevated in T2DM and DN patients compared to HS. Notably, levels were particularly high in microalbuminuria and macroalbuminuria groups when compared to T2DM only and HS. These findings agreed with those of a study conducted by Gomaa et al. [20] on sixteen T2DM compared to 30 HS, who found that the SH3YL1 levels were significantly higher in the patients than in the HS. Additionally, research by Han et al. [21] indicated that SH3YL1 levels increased with the development of stages in patients with DN. Yoo et al. [10] showed a study examining the physiological and pathological events underlying the relationship between SH3YL1 and DN [10, 20, 21]. Furthermore, serum SH3YL1 levels were correlated with BU, SC, eGFR, and ACR, which play a significant role in the pathophysiology of kidney disease. SH3YL1 is inversely correlated with eGFR, indicating that higher protein levels are associated with severe kidney function. Meanwhile, in DN patients SH3YL1 levels positively correlate with ACR, indicating that an increase in SH3YL1 also increases albuminuria, a marker of renal damage. Other metabolic parameters such as BU are associated with elevated SH3YL1 levels, reflecting renal impairment and these results agree with previous studies [13, 20, 21].

Importantly, the results of the current study demonstrated that by ROC curve, SH3YL1 levels showed high accuracy for early discriminates of DN from T2DM at an AUC of 0.98. This result is consistent with previous findings by Gomaa et al. [20].

Yoo et al. [10], reported that upon stimulation of human embryonic renal cells expressing NOX4 cells, overexpression of SH3YL1 resulted in increased ROS generation compared to control cells, highlighting the critical role of the SH3YL1-NOX4 complex in glucose-induced oxidative stress in the renal system, which contributes to renal inflammation and fibrosis, ultimately leading to the development of DN [10, 14].

In a significant in vitro study by Choi et al. [13], it was described that renal affected by diabetes had upregulated expression of the SH3YL1 gene. This condition was accompanied by progressively higher levels of SH3YL1 expression in diabetic kidneys. SH3YL1 synthesis was increased under high glucose conditions and angiotensin II stimulation. It may be hypothesised that chronic hyperglycaemia and activation of angiotensin II in diabetics persistently stimulate SH3YL1 synthesis [12], and these changes may explain the elevated SH3YL1 levels observed in patients with DN [20]. There are some limitations to this study, including its case-control design, single-centre nature, and relatively small sample size. Furthermore, certain potential risk factors influencing DN such as molecular and hemodynamic factors, and waist-to-hip ratio were not collected through the methodology. Serum protein levels were not measured in patients with varying treatment periods. Additionally, none of the inflammatory markers were evaluated, which could have provided more information on the link between SH3YL1 protein and DN in patients.

CONCLUSION

SH3YL1 may serve as a predictor biomarker in DN, particularly in cases of macroalbuminuria. In addition, the interaction of SH3YL1 with routine biomarkers of DN reflects that SH3YL1 has emerged as a potential biomarker for renal outcomes. However, larger studies are required to confirm these findings. A better understanding of the role of SH3YL1 could establish it as a therapeutic target for DN.

ETHICAL DECLARATIONS

Acknowledgments

The authors are grateful to the laboratory attendants of the National Diabetes Center of Mustansiriyah University and their research assistants.

Ethics Approval and Consent to Participate

The study complies with the Helsinki Declaration and was approved by the local ethics committee of the National Diabetes Centre (October 20, 2023 Ref: NDSEC/15/345). All participants provided informed consent.

Consent for Publication

Not applicable (no personal information is published).

Availability of Data and Material

The datasets generated and analyzed during the study are available per request from the corresponding author.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

No funding.

Authors' Contributions

All authors contributed equally in the design and conception of the study. Mohammed NUG and Abd Al-Ghanny RG carried out the experiment. Mohammed NUG and Al-Shawk RS helped supervise the project. Mohammed NUG analysis the data. Mohammed NUG, Mutar SA, Omran HH and Oleiwi AR wrote the manuscript. All authors read and approved the final version of the manuscript.

REFERENCES

[1] N. Samsu. Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment. *BioMed research international*, 2021(1):1497449, 2021.

[2] N. A. Lefta, A. Y. Abed, and B. A. Abed. Estimation of asprosin levels in female Iraqi patients with type 2 diabetes and hypothyroidism. *J Med Chem Sci*, 6(2):433–439, 2023.

[3] N. M. Selby and M. W. Taal. An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. *Diabetes, Obesity and Metabolism*, 22:3–15, 2020.

[4] E. A. A. Abass, B. A. Abed, and S. N. Mohsin. Study Of Lysyl Oxidase-1 And Kidney Function In Sera Of Iraqi Patients With Diabetic Nephropathy. *Biochem. Cell. Arch.*, 21(1):1129–1132, 2021.

[5] L. Deng, W. Li, and G. Xu. Update on pathogenesis and diagnosis flow of normoalbuminuric diabetes with renal insufficiency. *Eur. J. Med. Res.*, 26(1):144, 2021.

[6] L. O. Farhan, B. A. Abed, G. J. Kashtl, and I. N. Salman. Insulin Like Growth Factor Binding Protein 7 as a Novel Diagnostic Marker in Sera of Iraqi Patients with Acromegaly. *Baghdad Science Journal*, 20(3):0979, 2023.

[7] B. S. Ajilore and B. O. Ajilore. Biomarkers of Diabetes-Induced Nephropathy. In Vinood B Patel and Victor R Preedy, editors, *Biomarkers in Diabetes*, pages 891–908. Springer International Publishing, 2023.

[8] B. A. Abed, I. N. Salman, E. A. Hassan, and N. U. G. Mohammed. Role of stanniocalcin-1 and proenkephalin-A as novel biomarkers in prediction of newly diagnosed type 2 diabetic patients. *Int. J. Diabetes Dev. Ctries.*, pages 1–7, 2024.

[9] Y.-C. Cheng, C.-L. Lu, C.-Y. Hsu, M.-L. Sheu, and I.-T. Lee. Urinary non-albumin protein-creatinine ratio is an independent predictor of mortality in patients with type 2 diabetes: a retrospective cohort study. *Scientific Reports*, 14(1):10526, 2024.

[10] J.-Y. Yoo *et al.* LPS-induced acute kidney injury is mediated by Nox4-SH3YL1. *Cell Reports*, 33(3), 2020.

[11] T. Pecchillo Cimmino, R. Ammendola, F. Cattaneo, and G. Esposito. NOX dependent ROS generation and cell metabolism. *Int. J. Mol. Sci.*, 24(3):2086, 2023.

[12] A. Vermot, I. Petit-Härtlein, S. M. E. Smith, and F. Fieschi. NADPH oxidases (NOX): an overview from discovery, molecular mechanisms to physiology and pathology. *Antioxidants*, 10(6):890, 2021.

[13] G. S. Choi *et al.* SH3YL1 protein as a novel biomarker for diabetic nephropathy in type 2 diabetes mellitus. *Nutrition, Metabolism and Cardiovascular Diseases*, 31(2):498–505, 2021.

[14] S. R. Lee *et al.* Nox4-SH3YL1 complex is involved in diabetic nephropathy. *Iscience*, 27(2), 2024.

[15] American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2020. *Diabetes care*, 43(Supplement 1):S14–S31, 2020.

[16] E. O'Meara, K. S. Chong, R. S. Gardner, A. G. Jardine, J. B. Neilly, and T. A. McDonagh. The Modification of Diet in Renal Disease (MDRD) equations provide valid estimations of glomerular filtration rates in patients with advanced heart failure. *European journal of heart failure*, 8(1):63–67, 2006.

[17] A. N. Friedman *et al.* Value of urinary albumin-to-creatinine ratio as a predictor of type 2 diabetes in prediabetic individuals. *Diabetes care*, 31(12):2344–2348, 2008.

[18] F. Q. Nuttall. Body Mass Index: Obesity, BMI, and Health: A Critical Review. *Nutrition today*, 50(3):117–128, 2015.

[19] K. P. Suresh and S. Chandrashekara. Sample size estimation and power analysis for clinical research studies. *J. Hum. Reprod. Sci.*, 5(1):7–13, 2012.

[20] S. N. S. Gomaa, R. E.-S. Sheir, H. M. Farhan, T. M. Ahmed, and A. S. Abdelsattar. Assessment of SH3YL1 protein as a marker for diabetic nephropathy in type 2 diabetes mellitus. *Egyptian Journal of Medical Research*, 3(3):222–237, 2022.

[21] S. Y. Han, S. H. Han, J. Y. Ghee, J. J. Cha, Y. S. Kang, and D. R. Cha. SH3YL1 Protein Predicts Renal Outcomes in Patients with Type 2 Diabetes. *Life (Basel, Switzerland)*, 13(4):963, 2023.

http://doi.org/10.33091/amj.2025.154918.1982