Current Science International
Volume: 12 | Issue: 04| Oct. – Dec.| 2023

EISSN:2706-7920 ISSN: 2077-4435
DOI: 10.36632/csi/2023.12.4.41
Journal homepage: www.curresweb.com
Pages: 575-584

Assessment of Urinary Periostin Level as a Predictor of Nephropathy in Patients with Type 2 Diabetes Mellitus

Sara A. I. Yassien[1], Sahar S. El-Din Zaki Bessa[1], Maaly M. Mabrouk[2] and Mohamed S. Aboelnasr[1]

[1]Internal medicine department, Faculty of medicine, Tanta University, Tanta, Egypt
[2]Clinical Pathology department, Faculty of medicine, Tanta University, Tanta, Egypt

Received: 11 Sept. 2023 **Accepted:** 18 Oct. 2023 **Published:** 15 Nov. 2023

ABSTRACT

Background Periostin, originally identified in osteoblasts, functions as a cell adhesion molecule for pre-osteoblasts. It is categorized as a soluble extracellular matrix protein of 836 amino acids in length. Periostin is not observed in adult kidneys under normal conditions. It was prominently expressed in tubulointerstitial areas during renal injury and its urinary level indicates the loss of renal tubular cells in response to diverse renal injuries. Presently, information regarding the role of periostin in chronic kidney diseases remains scarce. This study aims to clarify the potential role of urinary periostin as a predictor of nephropathy in patients with type 2 diabetes mellitus and to evaluate its relation to clinical and laboratory parameters. **Methods:** This study was carried out on 60 type 2 diabetic patients, divided according to urinary albumin/creatinine ratio into 20 with normoalbuminuria, 20 with microalbuminuria and 20 with macroalbuminuria. Also, 20 healthy subjects were included as a control group. Urinary periostin level, glycosylated hemoglobin, urinary albumin/creatinine ratio and serum creatinine were measured. Estimated glomerular filteration rate (eGFR) was calculated. **Results:** The mean urinary periostin level was statistically significantly higher in patients with macroalbuminuria as compared to the control, normoalbuminuria & microalbuminuria groups. Also, the mean urinary periostin level was statistically significantly higher in patients with microalbuminuria as compared to the control & normoalbuminuria groups. Moreover, it was statistically significantly higher in normoalbuminuric group as compared to control group. Urinary periostin level was positively correlated with duration of diabetes, fasting and postprandial blood glucose levels, glycosylated hemoglobin, urinary albumin/creatinine ratio, serum creatinine, total cholesterol and triglycrides but negatively correlated with eGFR. **Conclusion:** An increased urinary periostin level is considered as an early predictor for deterioration of renal function in diabetic patients, suggesting that periostin can be used to identify diabetics at risk for diabetic kidney disease development. Clearly, further well-designed prospective studies are required to prove this hypothesis.

Keywords: Periostin, Type 2 diabetes, Diabetic nephropathy

1. Introduction

Diabetes mellitus is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (Punthakee *et al.,* 2018).

Diabetic nephropathy (DN) has become the most common cause of chronic kidney disease and the first cause of dialysis initiation in the Western world, with the same trend observed in developing countries. It is characterized pathophysiologically by glomerular hypertrophy, hyperfiltration and microalbuminuria that over the course of years leads to progressive glomerulosclerosis, proteinuria, and decline in renal function (Schrijvers *et al.,* 2004).

Corresponding Author: Sara A. I. Yassien, Internal medicine department, Faculty of medicine, Tanta University, Tanta, Egypt.

In addition to glomerular pathology, DN involves tubulointerstitial compartment causing the expansion of tubular basement membranes, tubular atrophy, interstitial fibrosis and arteriosclerosis (Zhou *et al.,* 2008). Moreover, it has been proposed that tubular injury could precede glomerular injury which may explain the early increase in several urinary biomarker excretion compared with albumin. Improving the early detection of DN remains a great challenge in disease management (Satirapoj *et al.,* 2015).

Periostin, originally identified in osteoblasts, functions as a cell adhesion molecule for pre-osteoblasts. It is categorized as a soluble extracellular matrix protein of 836 amino acids in length (Idolazzi *et al.,* 2017). Periostin is not observed in adult kidneys under normal conditions. It was prominently expressed in tubulointerstitial areas during renal injury and its urinary level indicates the loss of renal tubular cells in response to diverse renal injuries (Satirapoj *et al.,* 2012). Its histopathologic expression patterns in the kidney in situ suggests that periostin participates in the pathogenesis of renal disease in response to transforming growth factor-beta (TGF-β) and that blocking periostin expression protected animals from renal injury (Mael-Ainin *et al.,* 2014).

Presently, information regarding the role of periostin in chronic kidney diseases remains scarce (Jia *et al*., 2020). It has been shown to be expressed in cysts of epithelial cells in human autosomal dominant polycystic kidney (Wallace *et al.,* 2008). Periostin is highly upregulated during disease progression and inversely downregulated during regression in a model of hypertensive renal disease (Guerrot *et al.,* 2012). Also, the appearance of urinary periostin in chronic allograft nephropathy patients underscores its value as a potential biomarker for chronic progressive renal injury in transplant recipients (Satirapoj *et al.,* 2014) Moreover, some studies have demonstrated a link between periostin and diabetic vascular complications (Patel *et al.,* 2019; Ding *et al.,* 2018; Guan *et al.,* 2015).

In an attempt to clarify the potential role of periostin as an early predictor of DN in type 2 diabetic patients and to evaluate its relation to various clinical and laboratory parameters, this work was designed.

2. Methods

This study is a cross-sectional study that was carried out on eighty subjects. Sixty type 2 diabetic patients were selected from those admitted to the Internal Medicine Department, Tanta University Hospital. Twenty healthy subjects were included as a control group. They were classified into 4 groups: Group I (included 20 normal subjects as control group), group II (included 20 type 2 diabetic patients with normoalbuminuria, group III (included 20 type 2 diabetic patients with microalbuminuria & group IV (included 20 type 2 diabetic patients with macroalbuminuria).

All cases were subjected to the following: Full history taking, complete clinical examination, abdominal ultrasonography, fundus examination of the eyes and laboratory investigations including: Complete urine analysis, fasting blood glucose, postprandial glucose level, glycosylated hemoglobin (HbA1c %), lipid profile, urinary albumin/creatinine ratio, blood urea, serum creatinine, estimated glomerular filtration rate (Khanijou *et al.,* 2022) and urinary periostin level.

2.1. Estimation of urinary periostin level using ELISA

2.1.1. Principal of the assay

The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human Periostin (POSTN) in samples. Add Periostin(POSTN) to monoclonal antibody Enzyme well which is pre-coated with Human Periostin(POSTN) monoclonal antibody, incubation; then, add Periostin(POSTN) antibodies labeled with biotin, and combined with Streptavidin-HRP to form immune complex; then carry out incubation and washing again to remove the uncombined enzyme. Then add Chromogen Solution A, B, the color of the liquid changes into the blue, and at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the Human Substance Periostin(POSTN) of sample were positively correlated.

2.2. Statistical analysis

The collected data were organized, tabulated and statistically analyzed using the IBM SPSS Statistics for Windows, Version 27.0 (Armonk, NY: IBM Corp). In this study, the qualitative data were described using number and percentage.

Quantitative data were presented as mean and standard deviation (SD). In all applied tests, the P-values associated with test statistics indicated the significance level at which the null-hypothesis (the hypothesis of no difference) was rejected, and it was set at 0.05 so that P-values > 0.05 are statistically non-significant, P-values ≤ 0.05 are significant, and P-values < 0.001 are highly significant.

- Analysis of variance (ANOVA or F test).
- Kruskal-Wallis test (Z test).
- Receiver operating characteristic (ROC) analysis.
- Multivariate logistic regression analysis.

3. Results

Clinical and laboratory parameters of the studied groups: Different demographic and laboratory parameters of subjects in the studied groups are shown in Table 1. Figure 1 show that the mean urinary periostin level was statistically significantly higher in the normoalbuminuric group as compared to the control group and in those with microalbuminuria as compared to the control and normoalbuminuric groups. Also, it was statistically significantly higher in macroalbuminuric group as compared to the control, normoalbuminuric and microalbuminuric groups with p value (P < 0.001). In diabetic patients, there was a statistically significant positive correlation between periostin level and UACR (rs=0.866, p < 0.001) is shown in Fig. 2. However, there was a statistically significant negative correlation between periostin level with eGFR (rs=-0.713, P < 0.001) is shown in Fig. 3.

ROC curve analysis was performed to compare the cut off value of different parameters implicated in diabetic nephropathy (Fig. 4) showed that the area under the ROC curve of HbA1C% was (0.867), the best cut off value of HbA1C% was (>7.6) which denoted sensitivity (65.7%) and specificity (68%) with P value (p=0.020). As regard to eGFR, the area under the ROC curve of eGFR was (0.968), the best cut off of eGFR was (≤58) which denoted sensitivity (77.5%) and specificity (71%) with P value (p=0.040).

Table 1: Clinical and laboratory parameters of the studied groups

	Group I (Control) [*N*= 20]	Group II DM with (Normo) [*N*= 20]	Group III DM with (Micro) [*N*= 20]	Group IV DM with (Macro) [*N*= 20]	Test of Significance
Sex (F/M)	9/11	12/8	15/5	16/4	P=0.086
Age (Years)	61.70 ± 6.17	59.85 ± 6.60	55.95 ± 8.21	59.40 ± 8.68	P=0.114
bmi (kg/m^2)	27.31 ± 1.39	30.61 ± 1.36	30.66 ± 1.69	30.26 ± 2.18	p<0.001*
SBP (mmHg)	113.00± 8.18	120.50 ± 9.85	123.25 ± 11.95	125.50±13.27	**P=0.007***
DBP (mmHg)	75.50 ± 5.10	77.25 ± 6.38	79.75 ± 6.58	82.75 ± 8.35	**P=0.012***
Duration of DM (years)	-	10.15 ± 2.96	11.30 ± 5.58	13.15 ± 3.92	P=0.060
Blood urea (mg/dl)	24.85 ± 6.34	39.05 ± 14.50	49.22 ± 14.51	62.75 ± 4.48	**p**<0.001*
Serum creatinine (mg/ dl)	0.69 ± 0.12	0.89 ± 0.16	1.35 ± 0.30	1.83 ± 0.56	**p**<0.001*
eGFR (ml/min/1.73 m2)	97.25± 11.53	80.05 ± 12.88	50.50 ± 15.78	32.45 ± 18.17	**p**<0.001*
UACR(mg/g cr)	14.97 ± 6.44	16.53 ± 6.15	111.51 ± 57.44	747.78± 374.74	**p**<0.001*
Fasting blood glucose level(mg/dl)	83.05 ± 6.44	125.35 ± 15.81	141.35 ± 39.97	226.55± 62.04	**p**<0.001*
2-hpostprandial glucose level (mg/dl)	128.40 ± 6.19	174.25 ± 31.87	209.40 ± 53.83	298.55 ± 81.94	**p**<0.001*
HbA1C (%)	5.20 ± 0.27	7.39 ± 0.59	8.02 ± 1.83	11.63 ± 2.26	**p**<0.001*
Triglycerides(mg/dl)	98.93± 16.08	104.18 ± 31.04	155.15 ± 47.81	178.30±99.92	**p**<0.001*
Total cholesterol (mg/ dl)	186.08±15.17	184.75 ± 43.30	216.15 ± 45.86	235.45±93.51	**P**=0.014*
HDL-C (mg/dl)	67.60 ± 6.34	66.74 ± 16.70	59.22 ± 17.53	42.59 ± 10.79	**p**<0.001*
LDL-C (mg/dl)	99.35± 13.57	97.00 ± 37.62	126.72 ± 43.21	155.72±73.21	**P**=0.002*
Periostin (ng/mL)	0.90 ± 0.59	4.17 ± 2.50	12.08 ± 3.55	18.28 ± 2.90	**p**<0.001*

Data are presented as mean+SD, *Statistically significant difference, DM diabetes mellitus, BMI Body mass index, SBP Systolic blood pressure, DBP Diastolic blood pressure, HbA1C Glycated haemoglobin, eGFR Estimated Glomerular filtration rate, U Urinary, ACR albumin-to-creatinine ratio, HDL-C High-density lipoprotein- cholesterol, LDL-C Low density lipoprotein-cholesterol

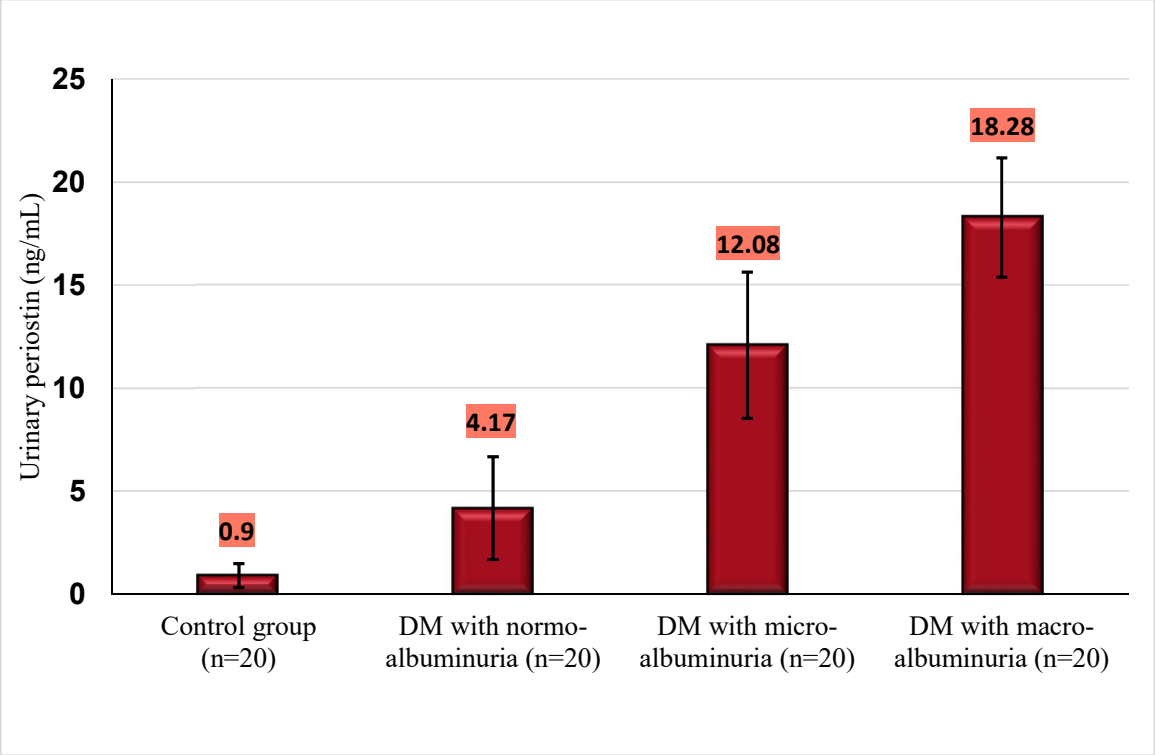

Fig. 1: Mean urinary periostin levels in the studied groups

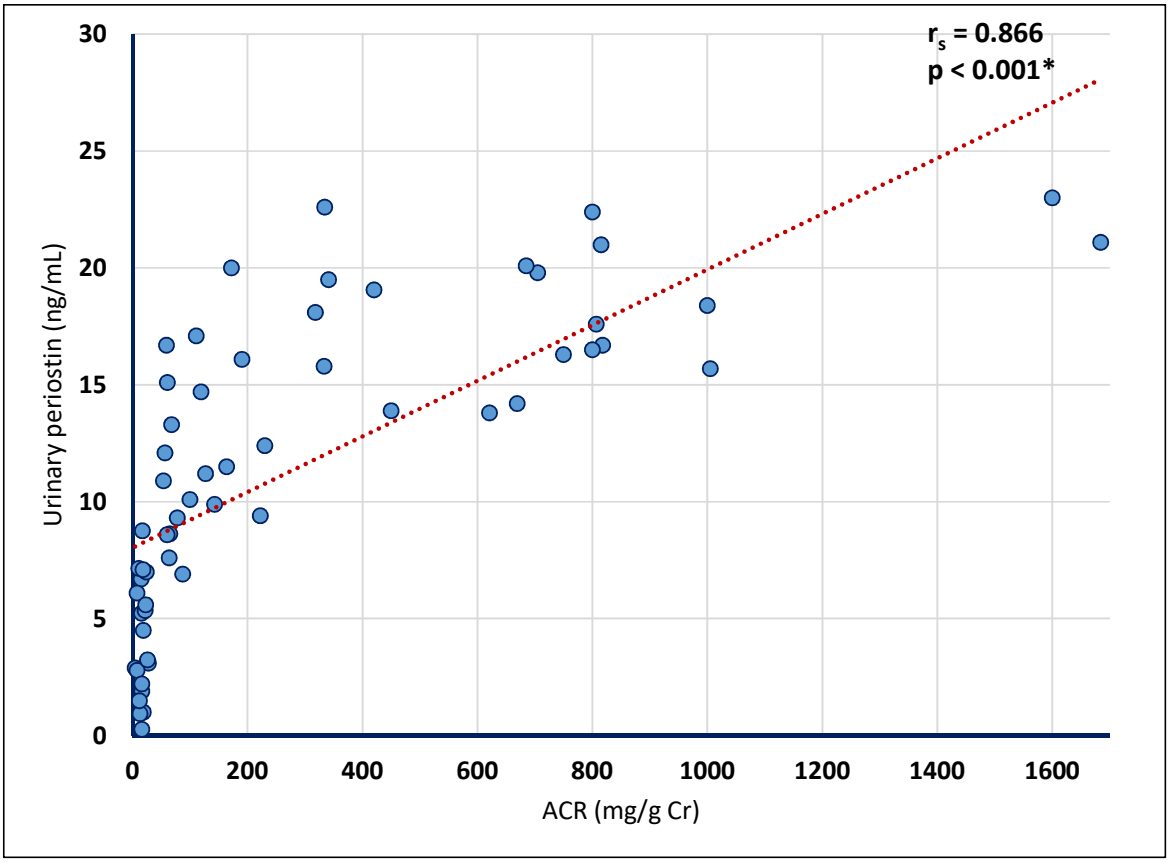

Fig. 2: Correlation between the albumin/creatinine ratio (ACR) and the urinary periostin level in type 2 diabetic patients

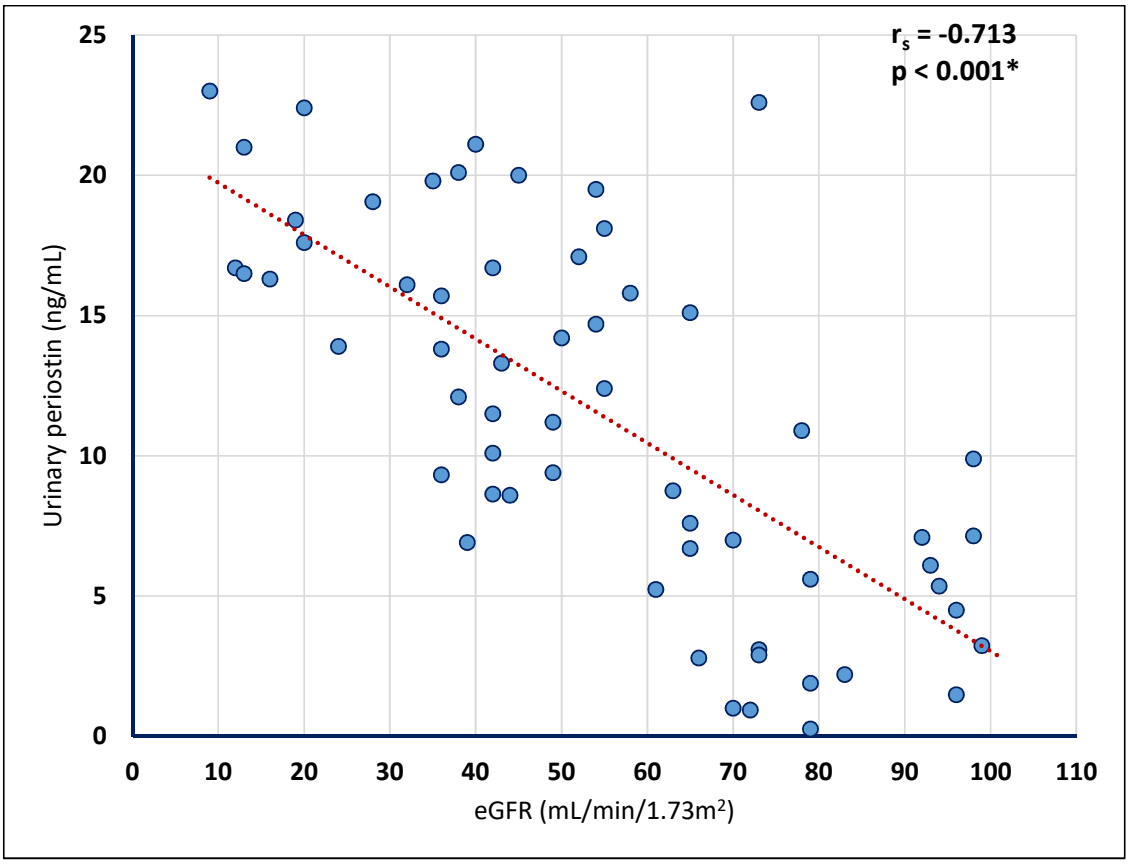

Fig. 3: Correlation between the eGFR and the urinary periostin level in type 2 diabetic patients

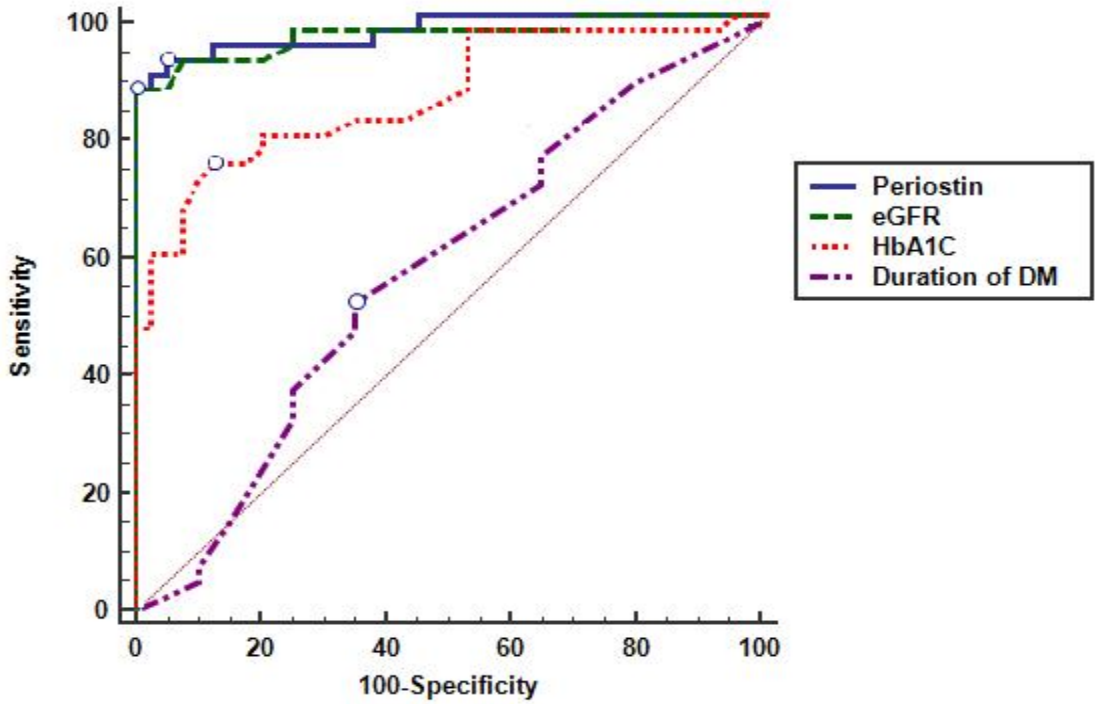

Fig. 4: ROC curve analysis of urinary periostin, eGFR, HbA1c & duration of DM implicated in the pathogenesis of diabetic nephropathy

As regard to periostin, the area under the ROC curve of periostin was (0.974), the best cut off of periostin was (>7.15) which denoted sensitivity (92.5%) and specificity (75%) with P value (p<0.001). The area under the ROC curve (AUC) of periostin for detecting diabetic nephropathy was significantly larger than that of HbA1C% and estimated glomerular filteration rate proving that periostin is an excellent predictive biomarker and very sensitive parameter for diabetic nephropathy.

The multivariate logistic regression analysis was performed to test for independent predictors of diabetic nephropathy. The model included the important parameters implicated in the pathogenesis of renal impairment in type 2 diabetic patients. Periostin, eGFR, HbA1C% and DM duration. The logistic regression coefficient of periostin (β=0.916, p < 0.001), eGFR (β=-0.690, p=0.006), HbA1C% (β=0.260, p=0.022) & DM duration (β=0.132, p=0.041). This analysis demonstrated that periostin is an independent predictor for diabetic nephropathy in type 2 diabetic patients was shown in Table 2.

Table 2: Multivariate logistic regression analysis of predictors of nephropathy among type 2 diabetic patients

	β	S.E.	Exp (B)	95% C.I.for Exp (B)	p-value
Urinary periostin (ng/ml)	0.916	0.220	1.847	0.944 - 1.000	<0.001*
e GFR(mL/min/1.73m^2)	-0.690	0.041	1.335	0.929 - 1.000	0.006*
HbA1C (%)	0.260	0.037	1.190	0.787 - 0.947	0.022*
Duration of DM (years)	0.132	0.046	1.129	0.418 - 0.737	0.041*

B: standard coefficient CI: confidence interval * significant at p≤0.05

4. Discussion

Diabetic kidney disease is expected to increase rapidly over the coming decades with rising prevalence of diabetes worldwide. Current measures of kidney function based on albuminuria and estimated glomerular filtration rate do not accurately stratify and predict individuals at risk of declining kidney function in diabetes. As a result, recent attention has turned towards identifying and assessing the utility of biomarkers in diabetic kidney disease (Khanijou *et al.,* 2022).

Diabetic nephropathy (DN) is the most common leading cause of end-stage renal disease in type 2 diabetes. Although major advances have been made in uncovering the mechanism of DN, the exact pathophysiology remains incompletely understood (Schrijvers *et al.,* 2004). In addition to glomerular pathology, DN involves tubulointerstitial compartment causing the expansion of tubular basement membranes, tubular atrophy, interstitial fibrosis and arteriosclerosis (Zhou *et al.,* 2008). Moreover, it has been proposed that tubular injury could precede glomerular injury which may explain the early increase in several urinary biomarker excretion compared with albumin. Improving the early detection of DN remains a great challenge in disease management(Oshima *et al.,* 2002).

Periostin, named after its expression in the periosteum of long bones, is a 90 kDa extracellular matrix protein of 836 amino acids. It is also expressed in many other tissues and organs, including heart, kidneys, skin and lungs, being enhanced by mechanical stress or injury (Idolazzi *et al.,* 2017*)*. Periostin is not observed in adult kidneys under normal conditions. It was prominently expressed in tubulointerstitial areas during renal injury and its urinary level indicates the loss of renal tubular cells in response to diverse renal injuries(Satirapoj *et al.,* 2012).

Presently, information regarding the role of periostin in chronic kidney diseases remains scarce (Jia *et al.,* 2020). It has been shown to be expressed in cysts of epithelial cells in human autosomal dominant polycystic kidney (Wallace *et al.,* 2008). Periostin is highly upregulated during disease progression and inversely downregulated during regression in a model of hypertensive renal disease (Guerrot *et al.,* 2012). Also, the appearance of urinary periostin in chronic allograft nephropathy patients underscores its value as a potential biomarker for chronic progressive renal injury in transplant recipients (Satirapoj *et al.,* 2014). Moreover, some studies have demonstrated a link between periostin and diabetic vascular complications (Patel *et al.,* 2019; Ding *et al.,* 2018; Guan *et al.,* 2015).

The present study was conducted to clarify the potential role of periostin as a predictor of DN in type 2 diabetic patients and to evaluate its relation to various clinical and laboratory parameters.

In the current study, the mean urinary periostin level was statistically significantly higher in patients with macroalbuminuria as compared to the control, normoalbuminuria & microalbuminuria

groups. Also, the mean urinary periostin level was statistically significantly higher in patients with microalbuminuria as compared to the control & normoalbuminuria groups. Moreover, it was statistically significantly higher in normoalbuminuric group as compared to control group. Urinary periostin level was positively correlated with duration of diabetes, blood pressure, fasting blood glucose, 2-hour post prandial blood glucose, glycosylated hemoglobin percentage, urinary albumin/creatinine ratio, serum urea, serum creatinine, total cholesterol, LDL-C and triglycrides but negatively correlated with eGFR and HDL-C. In the current study, the diagnostic value of urinary periostin in identifying DN was demonstrated by using the ROC curve analysis. The best cut off point of urinary periostin was >7.15 ng/dL with 92.5% sensitivity and 75% specificity.

These results are in agreement with Patel *et al.* (2019), who measured the association of urinary periostin level in type 2 diabetic subjects and healthy controls and evaluated its predictive value to diagnose renal injury. The study revealed that increased levels of urinary periostin significantly correlated with aging, high albuminuria, decline of eGFR and can be detected in the urine of the patients with type 2 diabetes before the onset of significant albuminuria. In type 2 diabetics with normoalbuminuria, urinary periostin levels were significantly higher than in controls and urinary periostin excretion correlated with the severity of nephropathy in patients with type 2 diabetes. Elevated periostin levels in the urine suggests that it can be used for early diagnosis and advanced interventions in type 2 diabetes.

These findings are supported by Satirapoj *et al.* (2015), who found that urinary periostin levels were significantly elevated in diabetic patients compared with healthy controls. Increased urine periostin level significantly correlated with aging, high albuminuria and decline of GFR. Urine periostin ELISA also demonstrated high performance for the diagnosis of established normoalbuminuric, microalbuminuric and macroalbuminuric type 2 diabetes. Moreover, the study indicates that increased urinary periostin levels can be detected in patients with type 2 diabetes before the onset of significant albuminuria.

It is worth noting that the current study was in harmony with a recent finding by Taha *et al.* (2022), who assessed urinary periostin in controlled and uncontrolled diabetics and found that urinary periostin showed a significant increase in uncontrolled diabetics. Urinary periostin was demonstrated as a more preferable biomarker being a non-invasive sample for predicting renal insult in diabetic subjects. This biomarker could be performed regularly for early detection of DN.

Within the same context, Qamar El-Dawla *et al.* (2019), discussed the value of periostin as a biomarker of DN development which showed that serum periostin was highly correlated with the severity of DN with slight difference between normoalbuminuria and control groups & highly significant increase in other remaining groups than control group reaching the highest value in macroalbuminuria group. There was significant positive correlation between levels of periostin and both UACR and urea.

Recently, Abbad *et al.,* (2022), investigated the contribution of periostin and its interaction with nuclear factor-kappa B(NF-κB) in experimental model of DN and found that increased periostin expression was correlated with decreased renal function, advanced stage renal damage and fibrosis, and NF-κB activation. Subsequently, they identified novel pathways and genes regulated by the NF-κB-periostin interaction which are involved in the mechanisms of progression of DN. Some of these genes, such as Fibroblast growth factor 1 (FGF1) and Growth differentiation factor 15 (GDF15), have the potential to be new biomarkers and/or targets for the therapy of DN.

On the other hand, Ding *et al.* (2018), [13] demonstrated that serum periostin is significantly associated with the presence of diabetic retinopathy in patients with type 2 DM and is an independent risk factor of diabetic retinopathy.

Reportedly, Wu *et al.* (2021), showed that in patients with glomerular disease urine POSTN/Cr was associated with higher urinary protein creatinine ratio (UPCR), UACR and lower eGFR. Additionally, urine POSTN/Cr was associated with increased acute tubular injury but was not associated with other morphological features such as global or segmental sclerosis, interstitial fibrosis, tubular atrophy or foot process effacement.

Another interesting data were presented by Aghamir *et al.* (2023), who studied the relationship between salivary and serum POSTN and renal function in patients with a history of a kidney transplant and found that salivary POSTN in normal function patients was significantly higher than

graft failure patients, concluding that salivary POSTN in patients with a history of kidney transplant could be a marker for the prognosis of renal function.

Additionally, in Duan *et al.* (2023), the animal and cell models of DN were constructed in streptozocin (STZ)-induced mice and high glucose-challenged human mesangial cells (HMCs). Interference of periostin reduced pathological changes, inflammation and renal fibrosis in diabetic kidney injury which provides a potential therapeutic target for DN.

Also of note, Um *et al.* (2017) evaluated the effect of periostin inhibition by an aptamer-based inhibitor on renal fibrosis under diabetic conditions. In vitro, transforming growth factor-β1 (TGF-β1) treatment significantly upregulated periostin, fibronectin, and type I collagen mRNA and protein expressions in inner medullary collecting duct (IMCD) cells. These increases were attenuated significantly in periostin-binding DNA aptamer (PA)-treated IMCD cells exposed to TGF-β1. In vivo, PA treatment attenuated the increased blood urea nitrogen levels in the diabetic mice significantly. These findings suggested that inhibition of periostin using a DNA aptamer could be a potential therapeutic strategy against renal fibrosis in diabetic nephropathy.

Furthermore, Mael-Ainin *et al.* (2014), showed that periostin was highly induced locally during renal disease and that its expression is associated with the development of renal lesions in wild type (wt) animals. In contrast, mice lacking periostin expression are protected against structural and inflammatory alterations which is probably caused by a dual mechanism: reduced inflammatory influx and decreased TGF-β signaling. A preservation of the renal function was also observed in a hypertensive model of CKD when periostin expression was inhibited by antisense oligodeoxynucleotide (AS ODN) administration which provides evidence indicating that periostin mediates renal disease progression and suggests that the inhibition of its synthesis and/or action can lead to a therapeutic approach for CKD.

Meanwhile, Muratsu *et al.* (2022), investigated the role of POSTN in a rhabdomyolysis mice model of AKI induced by an intramuscular injection of 50% glycerol & *found that* POSTN was highly expressed in the kidney through rhabdomyolysis and was a positive regulator of AKI. Targeting POSTN might propose a new therapeutic strategy against the development of acute renal failure.

Some limitation in our study should be addressed. Firstly, the total number of patients was small. The results could be more conclusive and more propagative if carried out with a larger population. Secondly, the study design is a cross-sectional, so we could not establish the role of periostin as a marker to monitor therapeutic response. Thirdly, we did not demonstrate periostin expression in renal tissue of diabetic nephropathy subjects. Further prospective studies are hence needed to evaluate the role of urinary perostin as a prognostic marker and as a marker for the monitoring of therapeutic response in diabetic patients.

5. Conclusion

From this work, it could be concluded that an increased urinary periostin level is considered as an early predictor for deterioration of renal function in diabetic patients, suggesting that periostin can be used to identify diabetics at risk for diabetic kidney disease development. Clearly, further well-designed prospective studies are required to prove this hypothesis.

Abbreviations

AKI	Acute kidney injury
AS ODN	Antisense oligodeoxynucleotide
CKD	Chronic kidney disease
DM	Diabetes mellitus
DN	Diabetic nephropathy
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FGF	Fibroblast growth factor
GDF	Growth differentiation factor
HbA1c	Glycated haemoglobin
HDL-C	High density lipoprotein-cholesterol
HMCs	Human mesangial cells
IMCD	Inner medullary collecting duct

kDa	Kilodalton
LDL-C	Low density lipoprotein-cholesterol
NF-κB	Nuclear factor-kappa B
POSTN	Periostin
STZ	Streptozocin
SZ-DN	Streptozotocin-induced diabetic nephropathy
TGF-β	Transforming growth factor-beta
UACR	Urinary albumin creatinine ratio
UPCR	Urinary protein creatinine ratio

References

Abbad, L., N. Prakoura, A. Michon, *et al.,* 2022. Role of periostin and nuclear factor-κB interplay in the development of diabetic nephropathy. Cells; 11:2212.

Aghamir, S., M. Amiri, G. Panahi, *et al.,* 2023. Salivary and serum periostin in kidney transplant recipients. PLoS One; 18:e0285256.

Ding, Y., Q. Ge, H. Qu, *et al.,* 2018. Increased serum periostin concentrations are associated with the presence of diabetic retinopathy in patients with type 2 diabetes mellitus. J Endocrinol Invest; 41:937– 45.

Duan, X., C. Chen, X. Liu, *et al.,* 2023. Interference of periostin attenuates pathological changes, proinflammatory markers and renal fibrosis in diabetic kidney injury. J. Gen. Genom., 1-9.

Guan, J., W.Q. Liu, M.Q. Xing, *et al.,* 2015. Elevated expression of periostin in diabetic cardiomyopathy and the effect of valsartan. BMC CardiovascDisord; 15:90.

Guerrot, D., J.-C. Dussaule, M. Mael-Ainin, *et al.,* 2012. Identification of periostin as a critical marker of progression/reversal of hypertensive nephropathy. PLoS One; 7:e31974.

Idolazzi, L., E. Ridolo, A. Fassio, *et al.,* 2017. Periostin: the bone and beyond. Eur. J. Intern. Med., 38:12–16.

Jia, Y.-Y., Y. Yu, and H.-J. Li, 2020. The research status and prospect of periostin in chronic kidney disease. Ren Fail; 42: 1166-72.

Khanijou, V., N. Zafari, M. Coughlan, *et al.,* 2022. Review of potential biomarkers of inflammation and kidney injury in diabetic kidney disease. J Diabetes Metab. Res. Rev., 38:e3556.

Mael-Ainin, M., A. Abed, S.J. Conway, *et al.,* 2014. Inhibition of periostin expression protects against the development of renal inflammation and fibrosis. J. Am. SocNephrol., 25: 1724–36.

Muratsu, J., F. Sanada, N. Koibuchi, *et al.,* 2022. Blocking periostin prevented development of inflammation in rhabdomyolysis-induced acute kidney injury mice model. Cells, 11:3388.

Oshima, A., H. Tanabe, T. Yan, *et al.,* 2002. A novel mechanism for the regulation of osteoblast differentiation: transcription of periostin, a member of the fasciclin I family, is regulated by the bHLH transcription factor, twist. J. Cell Biochem; 86:792-804.

Patel, M.L., R. Sachan, D. Pushkar, *et al.,* 2019. Urinary periostin as an early predictor of renal injury in diabetic kidney disease: A tertiary centre experience. Int J Med Public Health; 9:100-4.

Punthakee, Z., R. Goldenberg, and P. Katz, 2018. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can J. Diabetes, 42: S10-S15.

Qamar El-Dawla, N., A. Sallam, M. El-Hefnawy, *et al.,* 2019. E-cadherin and periostin in early detection and progression of diabetic nephropathy: epithelial-to-mesenchymal transition. J Clin Exp Nephrol., 23:1050-7.

Satirapoj, B., R. Witoon, P. Ruangkanchanasetr, *et al.,* 2014. Urine periostin as a biomarker of renal injury in chronic allograft nephropathy. Transplant Proc; 46:135- 40.

Satirapoj, B., S. Tassanasorn, M. Charoenpitakchai, *et al.,* 2015. Periostin as a tissue and urinary biomarker of renal injury in type 2 diabetes mellitus. PLoS One; 10: e0124055.

Satirapoj, B., Y. Wang, M.P. Chamberlin, *et al.,* 2012. Periostin: novel tissue and urinary biomarker of progressive renal injury induces a coordinated mesenchymal phenotype in tubular cells. Nephrol. Dial Transplant; 27: 2702–11.

Schrijvers, B.F., A.S. De Vriese, and A. Flyvbjerg, 2004. From hyperglycemia to diabetic kidney disease: the role of metabolic, hemodynamic, intracellular factors and growth factors/cytokines. Endocr Rev; 25: 971 – 1010.

Taha, M., H. Mahdy-Abdallah, E. Shahy, *et al.,* 2022. Preference between serum homocysteine and urinary periostin as early predictive biomarkers of renal dysfunction among uncontrolled diabetics. J Complement Integr Med; 19:399-405.

Um, J., J. Park, B. Nam, *et al.,* 2017. Periostin-binding DNA aptamer treatment attenuates renal fibrosis under diabetic conditions. J. Sci. Rep., 7:8490.

Wallace, D.P., M.T. Quante, G.A. Reif, *et al.,* 2008. Periostin induces proliferation of human autosomal dominant polycystic kidney cells through alpha V-integrin receptor. Am. J. Physiol. Renal. Physiol., 295: F1463–F1471.

Wu, Q., J. Troost, T. Dai, *et al.,* 2021. Kidney injury molecule-1 and periostin urinary excretion and tissue expression levels and association with glomerular disease outcomes. Glomerular diseases, 1:45-59.

Zhou, J., X. Chen, Y. Xie, *et al.,* 2008. A differential diagnostic model of diabetic nephropathy and non-diabetic renal diseases. Nephrol Dial Transplant; 23:1940-5.