CORRELATION BETWEEN CLINICAL AND PATHOLOGIC FEATURES OF DIABETIC NEPHROPATHY

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Background: Diabetic nephropathy is the most common cause of end stage renal disease in Thailand. Renal biopsy remains the gold standard investigation to diagnose and classify diabetic nephropathy.
Objectives: In this study, we aimed to evaluate the correlation between clinical parameters and renal pathology classification among patients with type 2 diabetic and nephropathy.
Methods: We conducted an observational study and enrolled 63 patients undergoing renal biopsy between 1 January 2014 and 31 December 2018. Pathologic classification established by the Renal Pathology Society was used to assess the severity of histologic lesions in diabetic nephropathy. Clinical parameters including age, sex, duration, presence of diabetic retinopathy, blood urea nitrogen, creatinine, urine protein creatinine ratio, fasting plasma glucose and hemoglobin A1C were collected.
Results: At the time of biopsy, mean age was 50.25±11.46 years. Median duration of diabetes mellitus was 10 years with interquartile range (IQR) 3.75-12.00 years, mean serum creatinine was 2.44 ± 1.31 mg/dL and estimated glomerular filtration rate was 22.41±12.16 mL/min/1.73 m^2. Based on the glomerular classification, 1 patient (1.6%) was in class I, 16 (25.3%) in class II, 25 (39.7%) in class III and 21 (33.3%) in class IV. Using multivariate analysis, class IV was associated with rising serum creatinine compared with class II [adjusted odds ratio (AOR)= 2.58; 95% CI= 1.13-5.89]. Patients with interstitial fibrosis and tubular atrophy (IFTA) <25%, 25-50% and >50% were observed in 10, 27 and 22 patients, respectively. Patients with IFTA >50% were significantly associated with duration of diabetes (OR=1.27; 95%CI=1.21-1.57), serum creatinine (OR=3.92; 95%CI=1.34-11.48) and urine protein (OR= 1.25; 95%CI=1.01-1.55) compared with patients with IFA<25%. Using multivariate analysis, only serum creatinine (AOR=3.48; 95%CI=1.23-12.65) was confirmed as independently correlated to IFTA >50% compared with IFTA <25%. A univariate analysis revealed no significant correlation between vascular indexes and renal function.
Conclusion: The results revealed that advanced glomerular lesions and high IFTA >50% correlated with impaired renal function in type 2 diabetic nephropathy.

Keywords: Diabetic nephropathy, Arteriolar hyalinosis, Interstitial fibrosis and tubular atrophy, Renal function

J Southeast Asian Med Res 2022: 6:e0113
https://doi.org/10.55374/jseamed.v6i0.113

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Received: 7 December 2021
Revised: 31 January 2022
Accepted: 10 February 2022

Introduction

Almost 40% of patients with type 2 diabetes in a nationwide cross-sectional study in Thailand presented impaired glomerular filtration rate.[1] Diabetic nephropathy is the major cause of end stage renal disease worldwide and exhibits a higher risk of mortality, mostly from cardiovascular complications.[2] Renal complications reflect a complex pathophysiology, whereby various genetic and environmental factors determine susceptibility and progression to end stage renal disease.[3] Renal pathology and structure defect are detected even at the onset of diabetes mellitus and further development of renal changes in advanced stages of diabetic nephropathy.[4] Renal biopsy remains the gold standard investigation to diagnose and classify diabetic nephropathy. Patients with type 2 and advanced nodular glomerulosclerosis have structural-functional relationships similar to type 1, and tubulointerstitial and mesangial expansion correlates with renal function. [5]

The Research Committee of the Renal Pathology Society developed a consensus classification of diabetic nephropathy.The classification is based on glomerular, tubulointerstitial and vascular lesions. This classification showed good interobserver agreement, improved problematic definitions of diabetic glomerulopathy and was easy to use in clinical practice.[6] One study documented that renal pathologic diagnosis showed a good predictor for renal prognosis in type 2 diabetes, [7] but limited studies have yet elucidated the correlation between renal pathologic and clinical parameters according to this classification system.[8] In this study, we aimed to identify the correlation between evidence-based clinical factors and renal pathologic findings according to Tervaert's pathologic classification among patients with diabetic nephropathy.[6]

Methods

The study was approved by the Ethics Committee of the Institute Review Board, Royal Thai Army. We collected patients with biopsy-confirmed diabetic nephropathy from January 2014 to December 2018 at Phramongkutklao Hospital. Enrolment criteria consisted of patients with type 2 diabetes as defined by the American Diabetes Association criteria [9] and documented diabetic nephropathy were enrolled in the study. The sample size was calculated at 82 patients to reach statistical power of 80%with a type I error of 5.[10] Exclusion criteria included other glomerular diseases and inadequate tissue biopsy with less than eight glomeruli. The study was conducted under the provisions of the Declaration of Helsinki and the protocol was approved by the local ethics committee. Informed consent was obtained at the time of registry enrollment.

Baseline clinical and laboratory data were collected at the time of biopsy. Clinical data were recorded for each patient at the time of biopsy including age, sex, weight, duration of disease and diabetic retinopathy. Laboratory variables including fasting plasma glucose, hemoglobin A1C (HA1C), urine examination, serum creatinine and urine protein creatinine ratio, were measured at the time of renal biopsy.

All histologic diagnoses were sent to a single renal pathologist, unaware of patients' clinical data, to evaluate the biopsies according to Tervaert's pathologic classification.[6] The glomerular classification was as follows: class I, only glomerular basement membrane (GBM) thickening; class II, mesangial expansion; class III, nodular sclerosis and class IV, global glomerulosclerosis in more than 50% of glomeruli. Interstitial fibrosis and tubular atrophy (IFTA) scores were classified as follows: 0, absent; 1, less than 25; 2, 25 to 50% and 3, greater than 50% of the total area. Interstitial inflammation was scored as follows: 0, absent; 1, inflammation only in relation to IFTA and 2, inflammation in areas without IFTA. Arteriolar hyalinosis was scored as follows: 0, absent; 1, hyalinosis present in a minimum of one arteriole; and 2, more than one arteriole present in the total area. Arteriosclerosis was scored in the most severely affected artery as follows: 0, no intimal thickening; 1, intimal thickening less than the thickness of the tunica media and 2, intimal thickening greater than the thickness of the tunica media. For every patient, the histologic slides included hematoxylin and eosin, periodic acid–Schiff, Masson trichrome and periodic acid methenamine silver stains for light microscopy.

The study exclusively analyzed morphologic data; however, immunofluorescence (IgG, IgA, IgM, C3, C1q, fibrinogen, kappa and lambda light chains) was always performed to confirm the central diagnosis.

Statistical analysis

Descriptive data with mean ± standard deviation and median with interquartile range (IQR) were expressed on the histologic and clinical data collected at the time of biopsy. The Chi-square was used for categorical variables comparing renal histologic groups. The independent t-test, one-way analysis of variance, Mann-Whitney U and Kruskal-Wallis tests were used for continuous variables comparing renal histologic groups. Univariate and multivariate logistic regression analyses were performed to identify clinical factors associated with severity of renal pathologic changes in diabetic nephropathy. Statistical analysis was performed using SPSS Software (SPSS, Version 20, Chicago, IL, USA). All tests were two-sided with a significance level of 0.05.

Results

A total of 63 patients with biopsy-proven diabetic nephropathy were enrolled in the study. The patients were male (n=22, 34.9%), mean age at renal biopsy was 50.25±11.46 years and the median onset of type 2 diabetes preceding the time of renal biopsy was 10 years with IQR 3.75 to 12.00 years. The baseline renal profiles included urine protein creatinine ratio of 7.3 with IQR 4.7-11.3 g/gCr, BUN of 32.85±16.50 mg/dL, serum creatinine of 2.44±1.31 mg/dL and HA1C of 7.83±2.16%. The glomerular and IFTA classification, 33.3, 39.7, 25.3 and 1.6% of patients comprised classes IV, III, II and I, respectively and 34.9, 42.9 and 15.9% had IFTA <25%, 25 to 50% and >50, respectively. For one patient in glomerular class I, electron microscopy confirmed GBM thickening according to Tervaert's pathologic classification. The baseline clinical characteristics are summarized in **Table 1**.

Table 1. Characteristics of enrolled patients

Clinical characteristic	n = 63
Male	22 (34.9%)
Age± SD (years)	50.25±11.46
Median duration of DM (years)	10 (3.75 to 12.00)
Diabetic retinopathy	45 (71.4%)
BUN (mg/dL)	32.85±16.50
Creatinine (mg/dL)	2.44±1.31
Estimated glomerular filtration rate (mL/min/1.73 m^2)	22.41±12.16
Median urine protein creatinine ratio (g/g Creatinine)	7.3 (4.7 to 11.3)
Fasting plasma glucose (mg/dL)	165.6±82.1
Hemoglobin A1C (%)	7.83±2.16
Diabetic nephropathy	
Class I	1 (1.6%)
Class II	16 (25.4%)
Class III	25 (39.7%)
Class IV	21 (33.3%)
Interstitial fibrosis and tubular atrophy (IFTA) (N=59)	
< 25%	10 (16.9%)
25-50%	27 (45.7%)
> 50%	22 (37.2%)

Table 1. Characteristics of enrolled patients (Continued)

Clinical characteristic	n = 63
Interstitial inflammation (N=59)	
Absent	1 (1.6%)
Infiltration only relation to IFTA	57 (96.6%)
Infiltration in areas without IFTA	1 (1.6%)
Arteriolar hyalinosis (N=63)	
Absent	2 (3.2%)
At least one area of arteriolar hyalinosis	12 (19.0%)
More than one area of arteriolar hyalinosis	34 (54.0%)
Inadequate tissue diagnosis	15 (23.8%)
Presence of large vessels arteriosclerosis (n=63)	
No intimal thickening	6 (9.5%)
Intimal thickening less than thickness of media	13 (20.6%)
Intimal thickening greater than thickness of media	15 (23.8%)
Not present	29 (46.0%)

Data presents as mean±SD, median with IQR and percentage

Comparisons of pathologic findings among the groups according to glomerular lesions are shown in **Table 2**. Significant differences were found in BUN and serum creatinine between IFTA<25%, 25 to 50% and >50% (**Table 3**). No significant differences were found regarding age, serum creatinine, urinary protein excretion rate or clinical factors between patients with and without arteriolar hyalinosis (**Table 4**). A significant difference was found in age and HA1C between patients with and without large vessel arteriosclerosis (**Table 5**). Overall, no clinical findings differed among class II, III and IV groups, except serum creatinine was significantly higher in class IV (3.4 with IQR=2.0-4.7) than those in class III (1.80 with IQR=1.49-2.75) and class II (1.93 with IQR=1.47-2.75) groups (p=0.003). The initial step using univariate analysis for all clinical factors associated with the glomerular classification was analyzed. On univariate analysis, and compared with glomerular class II, glomerular class IV was found to be significantly associated with serum creatinine (OR=2.37; 95%CI=1.21-4.65). Univariate analysis indicated that duration of type 2 diabetes (OR=1.27; 95%CI=1.03-1.57), serum creatinine (OR= 3.92; 95%CI=1.34-11.48) and urine protein creatinine ratio (OR=1.25; 95%CI=1.01-1.55) were associated with severity of IFTA >50 compared with IFTA<25%. (**Table 6**). However, concerning univariate analysis, presence of large vessels arteriosclerosis was found to be insignificantly associated with any clinical findings. (**Table 6**). Using multivariate analysis, only serum creatinine [adjusted OR (AOR)=3.48; 5%CI=1.23 to 12.65] was confirmed as independently correlated with IFTA >50% compared with IFTA <25 after adjusting for age, duration of type 2 diabetes, serum creatinine and urine protein creatinine ratio (**Table 7**).

Discussion

Renal biopsy is considered the gold standard to evaluate histologic findings and assess severity of diabetic nephropathy lesions. Renal pathology could provide additional information concerning patient outcomes. However, the relationship between clinical parameters and renal histologic findings remain controversial regarding the definitions of Tervaert's pathologic classification and limiting its use in clinical practice. The main finding in our study confirmed that advance glomerular lesions in class IV and high tubulointerstitial fibrosis scores (>50) were independently related factors to impaired renal function among Thai patients with diabetic nephropathy.

Table 2. Clinical findings according to glomerular classification

	Class II (n=16)	Class III (n=25)	Class IV (n=21)	*p*-value
Age (years)	52.31±15.24	48.84±9.62	50.57±10.72	0.264
Gender, male, N (%)	6 (37.5)	8 (32.0)	8 (38.1)	0.894
Duration of DM (years)	10.0 (5.0-18.0)	7.0 (1.0 -10.5)	10.0 (5.2 -12.0)	0.256
BUN (mg/dL)	26.0 (17.2-35.6)	28.0 (21.5 -43.5)	40.0 (25.7 - 44.5)	0.099
Creatinine (mg/dL)	1.93 (1.47-2.75)	1.80 (1.49 -2.75)	3.4 (2.0-4.7)*	0.003
Urine protein creatinine ratio (g/gCr)	6.74 (4.32 -7.62)	7.26 (4.85-12.65)	8.4 (5.7 -14.0)	0.189
Fasting plasma glucose (mg/dL)	154.0 (112.0-221.5)	137.0 (115.0 -175.0)	158.0 (103.0-212.0)	0.901
Hemoglobin A1C (%	7.6 (7.0-8.3)	6.85 (6.4 -8.2)	7.3 (6.8-8.8)	0.490
Diabetic retinopathy, N (%)	9 (56.3)	20 (80.0)	16 (76.2)	0.143

Data presents as mean±SD, median with IQR and percentage. *$p < 0.05$ versus class II.

Table 3. Clinical findings according to interstitial fibrosis and tubular atrophy

	IFTA <25% (n=10)	IFTA 25-50% (n=27)	IFTA >50% (n=22)	*p*-value
Age (years)	54.10±11.63	50.63±12.03	47.95±10.14	0.688
Gender, male, N (%)	1 (10)	11 (40.7)	8 (36.4)	0.205
Duration of DM (years)	4.5 (0.9 -10.0)	10.0 (2.0-12.5)	10.0 (6.7-12.2)	0.118
BUN (mg/dL)	20.6 (11.5-37.2)	25.7 (20.5-40.0)*	39.4 (25.3-45.5)*	0.038
Creatinine (mg/dL)	1.28 (0.81-2.08)	1.80 (1.60-2.60)*	2.96 (2.07-4.66)*	0.001
Urine protein creatinine ratio (g/gCr)	5.60 (1.17-7.57)	7.30 (5.50-12.90)	8.96 (5.59-13.2)	0.093
Fasting plasma glucose (mg/dL)	173.5 (120.5-208.7)	145.0 (121.0-183.0)	127.5 (103.2-205.7)	0.367
Hemoglobin A1C (%	7.65 (6.77-9.80)	7.10 (5.95-8.07)	7.30 (6.67-7.97)	0.564
Diabetic retinopathy, N (%)	5 (50)	19 (70.4)	18 (81.8)	0.222

Data presents as mean±SD, median with IQR and percentage. *$p < 0.05$ versus IFTA<25%.

Table 4. Clinical findings according to arteriolar hyalinosis

	Absent arteriolar hyalinosis (n=2)	At least one area (n=12)	More than one area (n=34)	*p*-value
Age (years)	52.00±8.48	51.42±13.05	49.41±11.43	0.617
Gender, male, N (%)	1 (50.0)	4 (33.3)	11 (32.4)	1.000
Duration of DM (years)	4.0-7.0	10.0 (2.0-14.0)	7.5 (2.0-10.0)	0.376
BUN (mg/dL)	8.8-14.9	26.4 (20.2-35.5)	33.5 (23.0 -45.5)	0.271
Creatinine (mg/dL)	1.1-1.4	1.80 (1.19-2.78)	2.25 (1.67-3.34)	0.202
Urine protein creatinine ratio (g/gCr)	2.80-5.91	6.87 (5.35-12.19)	7.5 (5.42-12.92)	0.680
Fasting plasma glucose (mg/dL)	104.0 -146.0	175.0 (130.7- 210.2)	152.0 (113.7-201.2)	0.341
Hemoglobin A1C (%	6.9 -8.0	8.0 (5.6-11.0)	7.2 (6.4 -8.3)	0.663
Diabetic retinopathy, N (%)	1 (50.0)	6 (50.0)	25 (73.5)	0.410

Data presents as mean±SD, median with IQR and percentage. Compared between arteriolar hyalinosis at least one area and arteriolar hyalinosis more than one area

Table 5. Clinical findings according to large vessels arteriosclerosis

	No intimal thickening (n=6)	Intimal thickening less than thickness of media (n=13)	Intimal thickening greater than thickness of media (n=15)	*p*-value
Age (years)	42.33±11.69	51.54±12.34*	50.33±7.45*	0.027
Gender, male, N (%)	1 (16.7)	2 (15.4)	5 (33.3)	0.488
Duration of DM (years)	8.5 (6.2-12.0)	3.0 (1.0-12.2)	7.0 (3.0-10.0)	0.427
BUN (mg/dL)	40.0 (17.9 -55.3)	28.0 (20.2-39.4)	31.5 (24.0-47.0)	0.639
Creatinine (mg/dL)	2.68±1.61	1.90±0.88	2.68±1.65	0.401
Urine protein creatinine ratio (g/gCr)	8.90 (6.40-9.03)	9.35 (6.25-13.90)	7.10 (4.41-11.29)	0.437
Fasting plasma glucose (mg/dL)	174.5 (118.2-251.0)	162.0 (151.0-195.0)	136.0 (103.0-212.0)	0.685
Hemoglobin A1C (%	6.0 (5.4-7.2)	7.0 (6.8-8.1)	8.1 (7.6-9.8)*	0.012
Diabetic retinopathy, N (%)	4 (66.7)	6 (46.2)	11 (73.3)	0.605

Data presents as mean±SD, median with IQR and percentage. *$p < 0.05$ versus no intimal thickening

Table 6. Univariate analysis of clinical factors associated with severity of glomerular class, IFTA and arteriolar hyalinosis

	Class IV vs. class II (OR with 95%CI)	*p*-value	IFTA >50% vs IFTA <25% (OR with 95%CI)	*p*-value	Arteriolar hyalinosis more than one area vs. at least one area (OR with 95%CI)	*p*-value
Age (years)	0.99 (0.94 to 1.04)	0.676	0.95 (0.88 to 1.02)	0.144	0.99 (0.93 to 1.04)	0.609
Gender, male, N (%)	1.03 (0.27 to 3.92)	0.970	5.14 (0.55 to 48.37)	0.152	0.96 (0.24 to 3.87)	0.950
Duration of DM (years)	0.96 (0.86 to 1.07)	0.420	1.27 (1.03 to 1.57)*	0.027	0.93 (0.83 to 1.04)	0.207
BUN (mg/dL)	1.06 (0.99 to 1.12)	0.056	1.06 (0.99 to 1.12)	0.084	1.04 (0.98 to 1.07)	0.485
Creatinine (mg/dL)	2.37 (1.21 to 4.65)*	0.012	3.92 (1.34 to 11.48)*	0.013	2.06 (0.99 to 1.09)	0.154
Urine protein creatinine ratio (g/gCr)+	1.19 (0.99 to 1.43)	0.061	1.25 (1.01 to 1.55)*	0.040	0.99 (0.86 to 1.14)	0.900
Fasting plasma glucose (mg/dL)	0.99 (0.59 to 12.02)	0.318	0.99 (0.99 to 1.00)	0.165	0.99 (0.99 to 1.01)	0.666
Hemoglobin A1C (%)	1.00 (0.72 to 1.39)	0.993	0.81 (0.55 to 1.19)	0.291	0.92 (0.69 to 1.21)	0.538
Diabetic retinopathy, N (%)	2.67 (0.59 to 12.02)	0.202	4.80 (0.79 to 28.90)	0.087	2.38 (0.52 to 10.86)	0.263

*$p < 0.05$ versus control group

Table 7. Multivariate analysis of clinical factors associated with severity of glomerular class, IFTA and arteriolar hyalinosis

	Class IV vs. class II (OR with 95%CI)	Class IV vs. class II (Adjusted OR with 95%CI)[a]	IFTA >50% vs IFTA <25% (OR with 95% CI)	IFTA >50% vs IFTA <25% (Adjusted OR with 95% CI)[a]
Age (years)	0.99 (0.94-1.04)		0.95 (0.88-1.02)	
Duration of DM years)	0.96 (0.86-1.07)		1.27 (1.03-1.57)*	
BUN (mg/dL)	1.06 (0.99-1.12)		1.06 (0.99-1.12)	
Creatinine (mg/dL)	2.37 (1.21-4.65)*	2.58 (1.13-5.89)*	3.92 (1.34-11.48)*	3.48 (1.23-12.65)*
Urine protein creatinine ratio (g/gCr)	1.19 (0.99-1.43)		1.25 (1.01-1.55)*	

*$p < 0.05$ versus control group

[a] adjusted for age, duration of type 2 diabetes, serum creatinine and urine protein creatinine ratio

The impact of clinical renal involvement on long term prognosis in type 2 diabetes has been described in several studies. Our results demonstrated that serum creatinine levels in glomerulopathic class IV were significantly greater than those in other glomerular classes in type 2 diabetes. These results agreed with several cross-sectional studies demonstrating the relationship of renal histologic lesions with clinical features among patients with diabetes and nephropathy.[11, 12] Nevertheless, one study showed no significant differences in renal survival rates between glomerular classes.[8] However, advanced diabetic glomerulosclerosis in class IV exhibited the lowest estimated glomerular filtration rate and the worst five-year renal survival rate among patients with type 2 diabetes.[7] Several studies indicated an association between the severity of renal histological injury and renal prognosis.[13-15] Thus, quantitative scoring of glomerulosclerosis according to Tervaert's pathologic classification might be beneficial in determining worsening renal outcomes.

Nodular glomerulosclerosis reflected an advanced stage of nephropathy. Patients with type 2 diabetes and Kimmelstiel-Wilson nodules or at least glomerular class III according to Tervaert's pathologic classification revealed elevated serum creatinine compared with patients without nodular glomerulosclerosis.[16] Our results did not demonstrate significantly increased serum creatinine levels in glomerular class III, compared with glomerular class II. Similar to one study, the nodular glomerulosclerosis index did not correlate to renal function and proteinuria.[17] Nodular glomerulosclerosis might be a weaker predictor of renal progression than established indicators such as IFTA score. Moreover, several patients showed that the severity of interstitial lesions did not correlate with glomerular lesions [18] and the classification of nodular glomerulosclerotic lesions might have been influenced by sampling bias due to the number of glomeruli obtained by renal biopsy. Further studies are needed to determine the pathophysiologic change and clinical significance of nodular glomerulosclerosis in type 2 diabetes.

Abnormalities in tubulointerstitial lesions are important when assessing the outcome of patients with type 2 diabetes.[19-21] Tervaert's pathologic classification focuses on tubular atrophy and interstitial fibrosis in diabetic nephropathy. The majority of patients (87.8%) included in our study had IFTA >25%; this renal chronicity score related to poor renal function and high proteinuria. The findings were consistent with related prospective studies that identified a correlation between the degree of tubulo-interstitial injury with renal function [22] and interstitial lesions as a predictor for renal prognosis among patients with type 2 diabetes and overt proteinuria.[8] Early identification of ITFA among patients with type 2 diabetes could prompt more therapeutic interventions.

Arteriosclerosis manifests itself as a lesion of the intimal layer of the arterial wall and accumulation of plaque [23] and develops as a result of a multistep process ultimately leading to cardiovascular disease in type 2 diabetes. [24] Several studies have documented the development of atherosclerosis related to aging and chronic hyperglycemia. [25, 26] Our study also confirmed that a significant difference was found in aging and uncontrolled glycemic with renal vessel arteriosclerosis.

The main limitation encountered was the relatively small sample size. In addition, a single-center prospective study of clinical and histopathologic lesions among patients with type 2 diabetes, indicated our study may have been underpowered to detect meaningful histopathologic lesions and subjects might not be representative of all populations in type 2 diabetes. Second, only the cross-section study was evaluated. A further study of renal pathologic scores with main renal outcomes including double serum creatinine and long term renal replacement therapy is needed. Third, a high percentage of inadequate tissue diagnosis for vascular lesion and a limited sample regarding the interstitial inflammation were found in this study. Therefore, they could have resulted from assessing the correlation of vascular and interstitial pathological lesions and clinical findings. More clinical studies based on renal biopsy are needed to clarify the correlation between vascular lesions and tubulointerstitial inflammation in diabetic nephropathy.

Conclusion

In conclusion, advanced diabetic glomerulosclerosis (class IV) and high percentage of IFTA (>50%) according to Tervaert's pathologic classification were significantly associated with impaired renal function among patients with type 2 diabetes and overt proteinuria. These results indicated that the advanced glomerular and IFTA pathologic classification correlated with renal outcome in type 2 diabetic nephropathy.

Acknowledgments

The authors would like to acknowledge the contributions of the staff, Division of Nephrology and Division of Pathology, Phramongkutklao Hospital.

Disclosures

All authors report no conflicts of interest associated with the study.

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