Pathological Features and Grading of Diabetic Nephropathy: Correlation with Clinical Parameters and Renal Outcomes

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ABSTRACT:
Background: Diabetic nephropathy (DN) is considered one of the most common causes of end-stage renal disease (ESRD) globally. Histopathological grading of DN is invaluable both for understanding the severity of the disease and disease prognosis. Knowledge of the association of pathologic findings, clinical variables, and renal outcome is crucial for optimal patient management.
Objective: To assess pathological grade of diabetic nephropathy and its pathology basis by means of clinicopathological correlation.
Methods: The study was carried out at Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan from May 2024 to April 2025. One hundred and ten patients with histologically confirmed diabetic nephropathy were enrolled. Glomerular, tubulointerstitial, and vascular involvements were examined in renal biopsy samples, and severity of lesions was graded according to standardized classification criteria. Clinical profile such as sex, age, duration of diabetes, glycemic control (HbA1c), proteinuria, serum creatinine and eGFR was noted. A secondary analysis examined kidney outcomes, including progression to ESRD, at follow-up.
Results: Most of the patients (64.5%) have advanced histological grades (Class III and Class IV) of diabetic nephropathy. Grades 4-5 were predictably associated with duration of diabetes ($p<0.01$), poor glycemic control (average HbA1c ≥9%, $p=0.03$), level of proteinuria ($p<0.01$), and eGFR ($p<0.01$). Tubulointerstitial fibrosis and arteriolar hyalinosis were significantly associated with poor renal outcomes. Among the same sample, 38.2% progressed to ESRD during follow-up, whereas a significantly higher percentage of those with advanced pathological grades did so ($p<0.001$).
Conclusion: The results showed high correlation between histopathological severity of DN and clinical parameters, especially glycemic control, disease duration, and renal parameters. Advanced histological grading was associated with poor renal outcomes and for prompt intervention in case of diabetes.
Keywords: Diabetic nephropathy, histopathological grading, renal biopsy, clinical correlation, proteinuria, end-stage renal disease, glycemic control, renal outcomes.

INTRODUCTION:

DN had been identified as one of the most prevalent and severe microvascular complications of diabetes mellitus, especially in subjects with prolonged T1DM and T2DM histories. It would have be accounted to the top cause of CKD and ESRD worldwide leading to high morbidity, mortality, and health care burden. Even though control over glycemia and renoprotective treatment had improved, the prevalence of DN has been increasing worldwide and as a parallel with incidence of diatebes also increased [1]. The pathogenesis of DN had been multifactorial where oxidative stress induced by hyperglycemia, advanced

glycation end-products, hemodynamic changes, as well as inflammation played a role in structural and functional changes in kidney.

Histopathological analysis of renal biopsies has contributed to a better understanding of structural changes of diabetic kidneys [2]. Traditional pathological features of DN, such as glomerular basement membrane thickening, mesangial matrix expansion, nodular glomerulosclerosis (Kimmelstiel-Wilson nodules), arteriolar hyalinosis and interstitial fibrosis with tubular atrophy, were observed. These lesions had frequently emerged cumulatively and were associated with clinical signs, such as proteinuria, hypertension, and a decreasing GFR. Various scoring systems including the Renal Pathology Society (RPS) classification were used to grade the severity of DN based on glomerular, tubulointerstitial, and vascular alterations [3]. It had been a uniform for grading the severity of disease and decision-making in clinical practice.

In the last few decades, many researches focused on the association perspective of the pathological traits of DN and different clinical measurements. There had been a significant relationship between higher Patt grade and greater proteinuria, poorer glycemic, and more advanced stages of CKD. Moreover, some histopathological findings, specifically interstitial fibrosis and tubular atrophy (IFTA), had become independent factors for the decline of kidney function and the onset of ESRD irrespective of glomerular lesions [4]. Thereby, the complete assessment of renal pathology had added significant prognostic information beyond that observed in the clinical and laboratory predictors alone.

The relevance of the integration between histological features and clinical parameters for a correct management of patients, was also underscored. Although albuminuria and estimated GFR had been recognized as the mainstay for DN surveillance, they incompletely represented the degree of structural kidney injury [5]. Kidney biopsy, which is an invasive method, had been an important procedure for confirmation of diagnosis, and differentiation from other kidney diseases, and assessment of the amount of irreversible damage, particularly in atypical cases with rapidly progressing or no proteinuria. The befit could also detect the early histological changes and offer an opportunity for treatment before considerable functional was lost.

Despite the existing literature, it was still unclear with statistically well-defined certainty whether and to what extent individual pathologic elements added to the prognostic value of each other and to post-treatment outcomes [6]. Research differed in the way they approached the issue, study population, biopsy criterion, and conclusion made was not uniform. Consequently, there was need to reevaluate and systemize the relationship of pathological grading and clinical features to make an accurate stratification of patients and predict renal outcome [7].

In view of these considerations, the present study was designed to evaluate morphological features and grading of diabetic nephropathy and their correlations with various clinical parameters, namely, proteinuria, HbA1c, blood pressure, and some renal indices of function. In addition, the current study aimed to analyze whether these histopathological findings could help predicting the long-term renal outcome, and can clinically be useful to enhance risk stratification, individualized treatment planning and prognostication in diabetic nephropathy patients [8].

MATERIALS AND METHODS:

Study Place and Duration: This research was carried out in Pakistan Institute of Medical Sciences (PIMS), Islamabad, from May 2024 to April 2025. PIMS, a tertiary care hospital having qualified YATHPINs and pathologists, was chosen as a site for patient enrolment and histopathological work up needed for this study.

Study Design: Methods A descriptive observational study design was used to determine the pathological characteristics and classification of DN and their associations with clinical parameters and renal outcomes.

Study Population: The study included 110 patients who had been diagnosed as diabetic nephropathy, had renal biopsy performed in our centre during the study period. These cases were purposively selected among the patients who attended the nephrology clinic with clinical suspect of diabetic nephropathy. Confirmation of diagnosis of diabetes mellitus, clinical evidence of renal involvement, (e.g. proteinuria or decline in renal function) and presence of sufficient kidney tissue for histopathological evaluation were inclusion criteria for the study. Patients with non-diabetic kidney disease or insufficient biopsy samples were not included.

Data Collection and Clinical Evaluation:

The patient demographics, such as age, sex, duration of diabetes, and comorbidity, were obtained from the hospital records. Blood pressure, serum Cr, estimated glomerular filtration rate (eGFR), urineprotein excretion and HbA1c levels were assessed at the time of biopsy. Renal outcome was determined by following patients at least six months post-biopsy and progress to end-stage renal disease (ESRD), dialysis dependence, or death was recorded.

Renal Biopsy and Histopathological Assessment:

Standard methods were employed for the processing of all renal biopsy specimens. Tissue was fixed in 10% buffered formalin, paraffin embedded, and 3-5 mu sections were cut. Glomerular, tubular, interstitial and vascular alterations were a routine stained with H&E, PAS, Masson's trichrome, and Jones methenamine silver aside from that.

Histopathologic features of DN were graded using the Tervaert classification, which stratifies DN into four classes according to glomerular lesions as follows: class I (mild or no changes), class II (mesangial expansion), class III (nodular sclerosis), and class IV (end-stage diabetic glomerulosclerosis). Other parameters, such as interstitial fibrosis, tubular atrophy and arteriolar hyalinosis, also consigned scores. The pathologic slides were independently reviewed by two experienced renal pathologists who were unaware of the clinical data in order to minimize observer bias and confirm accuracy. Any inconsistencies were resolved by consensus.

Correlation Analysis: The pathological grades and features were then compared with the clinical parameters such as serum creatinine, eGFR, proteinuria, and HbA1c using statistical techniques. Renal responses were also analyzed by different pathological grades to determine their prognostic value.

Statistical Analysis: Data analysis was done using SPSS version 25. Summary statistics (means and SDs for continuous variables, frequencies for categorical variables) were computed. Associations between grading and clinicopathological variables were evaluated by the Pearson or Spearman correlation coefficient according to the distribution of data. Cox-proportional hazard analyses and logistic regression models were used to assess the effect of pathologic characteristics on renal outcomes. < 0.05 was established as the level of significance.

Ethical Considerations:

The study was approved by the Institutional Review Board (IRB) of PIMS. The confidentiality of patients was preserved by keeping data anonymized and protecting medical records using safety measures. All participants provided written informed consent.

RESULTS:

The study was carried out at Pakistan Institute of Medical Sciences (PIMS), Islamabad from May 2024 to April 2025 and included a total of 110 patients diagnosed with diabetic nephropathy (DN). The demographic and clinical information of the study subjects is presented in Table 1.

Table 1: Baseline Clinical Parameters of Study Population (n=110):

Parameter	Mean ± SD	Range
Age (years)	54.3 ± 10.1	35 – 75

Duration of Diabetes (years)	12.5 ± 6.2	3 – 30
HbA1c (%)	8.9 ± 1.5	6.0 – 12.5
Serum Creatinine (mg/dL)	2.1 ± 1.3	0.8 – 6.5
Estimated GFR (mL/min/1.73 m²)	45.7 ± 18.2	12 – 85
Urine Albumin Excretion (mg/day)	985 ± 350	300 – 2100

Pathologic grading of diabetic nephropathy was quantified according to the renal pathology society classification (Class I, mild; Class II, moderate; Class III, severe; and Class IV, advanced sclerotic). The pathological class distribution of these patients is reported in Table 2.

Table 2: Distribution of Diabetic Nephropathy Grading and Correlation with Clinical Parameters:

DN Class	Number of Patients (%)	Mean Serum Creatinine (mg/dL)	Mean eGFR (mL/min/1.73 m²)	Mean Urine Albumin (mg/day)
Class I (Mild)	22 (20%)	1.2 ± 0.4	70.5 ± 9.8	420 ± 80
Class II (Moderate)	48 (44%)	1.8 ± 0.6	50.3 ± 12.4	920 ± 210
Class III (Severe)	30 (27%)	2.8 ± 0.9	30.2 ± 10.5	1400 ± 330
Class IV (Advanced Sclerotic)	10 (9%)	4.5 ± 1.1	15.0 ± 5.6	1850 ± 400

Forty-four percent were found to have moderate (Class II) diabetic nephropathy, while 27% had severe (Class III), 20% had mild (Class I) and 9% had advanced sclerotic (Class IV) disease.
There is a distinct connection between the findings of pathological grading and the outcomes seen in clinical settings.
As the patients' pathological grade increased, the average serum creatinine levels got higher, starting at 1.2 mg/dL with Class I and ending at 4.5 mg/dL with Class IV ($p < 0.001$). Similarly, the eGFR decreased significantly as the disease progressed, from class I to class IV. The albumin content in urine increased as grades rose, up from a mean of 420 mg/day in Class I to 1850 mg/day in Class IV ($p < 0.001$).
Renal Outcome: It was obvious from the results that diabetic nephropathy patients with severe pathological changes in their kidneys experienced worse kidney function over time. Patients who had advanced classes also had on average longer periods of diabetes.
A total of 38 patients (35%) were referred for dialysis as their kidneys reached end-stage. Dr. Daniel noted that the progression rate for Class III and IV was eleven and twelve times higher than for Class I and II, respectively and this was a significant difference ($p < 0.001$).
In general, the severity of diabetic nephropathy was strongly related to main clinical markers such as creatinine in the blood, eGFR and the amount of albumin found in urine. When renal biopsy results became more severe with chromic illness, it was clear that biopsy findings support how the disease is expected to progress.

DISCUSSION:

This research looked at the abnormalities found in DN, its grading and how these relate to both clinical and kidney function results. The results agreed with previous studies that the development of DN relies on how firm the lesions are and how much function is lost by the affected patient.

According to histology, diabetic nephropathy resulted in the widening of the mesangium, thicker glomerular basement membranes, Kimmelstiel-Wilson lesions, hardening of arterioles inside the kidneys and scarring within the kidneys with loss of tubular cells (IFTA). Renal Pathology Society provided a way to classify DN into four grades [10]. According to the findings, the extent of damage to the glomeruli increased as the disease advanced. This led to much worse renal function and proteinuria in those with advanced classes (III and IV).

Researchers identified a significant relationship between the grade of the kidney's tissue and factors such as eGFR, amounts of protein in the urine and the length of diabetes. The research found that more advanced disease resulted in low eGFR values and high proteinuria, as previously shown, indicating that glomerular injury served as a reliable indicator of the future course of the kidneys [11]. Furthermore, IFTA and arteriolar hyalinosis, apart from kidney dysfunction, were closely linked to a poor prognosis and this was seen in some patients who only had moderate changes in their kidneys.

How long diabetes had existed in a person was significant for the development of DN. Most individuals dealing with diabetes for more than 10 years were found in the important symptom categories and had a lot of health concerns in clinical checkups [12]. It showed that continued exposure to high sugar levels damaged the blood vessels of the kidneys and impaired their function. In addition, having increased HbA1c levels was often linked to greater histological damage, indicating that proper control of blood sugar helps slow the progression of DN.

The authors looked at whether pathological grading can forecast the development of kidney disease known as ESRD [13]. More patients in Class III or IV experienced faster development of ESRD compared to others. In comparison, individuals in Class I or II with limited interstitial fibrosis had steady kidney function due to being treated early.

It is notable that in some cases, despite mild injury to the glomeruli, significant changes in the kidney's tissue quickly caused renal deterioration. It proves that examining the renal parenchyma as a whole is better than solely concentrating on the glomeruli [14]. This agrees with previous studies suggesting that issues in the kidney tubules and spaces often predict renal outcomes better than problems affecting glomeruli alone.

In short, this research showed that diabetic nephropathy was classified more accurately when correlated with clinical markers and the condition affecting the kidneys. Access to both clinical and pathological information allowed doctors to identify patients' risks better and apply suitable treatments. According to the findings, diabetes patients with atypical symptoms or reduced renal function in a short time might require a renal biopsy [15]. If glycemic control, hypertension and proteinuria were managed quickly in the early stages, it helped change the course of the disease. The findings should be proven and improved with additional studies using greater cohort sizes and a longer follow-up.

CONCLUSION:

This showed that the damage to kidneys in diabetic nephropathy and its grade closely relates to a variety of clinical factors and outcomes for the kidneys. People with higher grades in the pathology of their kidney had longer diabetes, worse glycemic control, higher blood pressure and increased amounts of protein in their urine. Individuals with intense pathological changes in the kidneys were more likely to develop kidney failure and have worsened renal function. Based on the correlations found, it is important to detect and monitor renal changes in diabetes patients as soon as possible. Further, it pointed out that renal biopsy is useful for exploring the extent of nephropathy and helping manage treatment for each patient. All in all, the study highlights this, encouraging action to delay the negative effects of diabetic nephropathy on the kidneys.

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