

# Prevalence of Nondiabetic Glomerular Diseases in Patients with Type 2 Diabetes Mellitus

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## ABSTRACT

**Objective:** Despite notable progress made in the past decade in research and clinical practice in the treatment of diabetic kidney disease, the diagnostic and prognostic significance of proteinuria in patients with diabetes has imposed constant challenges to nephrologists and diabetologists. The main goal of the study was to assess the prevalence of nondiabetic kidney disease among proteinuric patients with type 2 diabetes mellitus.

**Methods:** We evaluated kidney biopsy findings obtained from 82 diabetic patients to assess the etiology of proteinuria.

**Results:** A review of histopathological results indicated features of diabetic nephropathy in 29 of these persons (36.7%). In 21 diabetic nephropathy patients (71.4%), proteinuria was within the nephrotic range. Nondiabetic kidney disease was discovered in 51 persons (62.2%), whereas in 2 cases, the exact type of glomerular disease has not been established.

**Conclusion:** We conclude from these results that diagnostic kidney biopsy is justified in type 2 diabetes patients with proteinuria since the prevalence of nondiabetic kidney disease is high in these subjects and adequate histopathological assessment could improve the management of their kidney disease.

**Keywords:** Proteinuria, diabetic nephropathy, glomerular disease, kidney biopsy

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## INTRODUCTION

Kidney biopsies have infrequently been performed in diabetic patients with kidney injury, based on the assumption that it predominantly results from diabetic nephropathy (DN) and histopathological evaluation of biopsy specimens is not helpful in the management of proteinuria in these individuals. Nonetheless, clinical suspicion of nondiabetic kidney disease (NDKD) remains valid mainly in atypical cases of DN, such as the sudden onset of severe proteinuria, short duration of diabetes, rapid decline of glomerular filtration, and absence of antecedent retinopathy. The latter is particularly characteristic for type 2 diabetes mellitus (T2DM), in which retinopathy is concordant with the development of glomerular disease in only 50%-60% of cases.<sup>1</sup> Moreover, structural changes in the nephropathy of T2DM are more

heterogeneous than in type 1 and they correlate less with clinical manifestations of kidney disease.<sup>2</sup> Kidney biopsy in T2DM patients with proteinuria has demonstrated that in many cases kidney injury is caused by NDKD, which could be managed better by a more personalized approach, including an option of immunosuppressive/anti-inflammatory therapy.<sup>3</sup> Therefore, we investigated the importance of NDKD in the pathogenesis of proteinuria in type 2 diabetic patients.

## METHODS

This retrospective study was approved by the Ethics Committee of Voivodship Specialty Hospital in Wrocław (15/02/2019, 2/2019). Because this has been a retrospective analysis of the data from medical records, no patient consent was obtained for participation in the



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study. Nevertheless, a written informed consent was obtained from each patient before the kidney biopsy.

We retrospectively evaluated the results of histopathological assessments, using routine light microscopic examination and immunofluorescence studies of kidney biopsy specimens, obtained from patients hospitalized at the Department of Nephrology, Voivodship Specialty Hospital in Wrocław in the years 2009-2018. Specimens of kidney cortices were processed and light microscopy/immunofluorescence images were examined at the Department of Pathology of Voivodship Specialty Hospital in Wrocław, as part of a routine diagnostic procedure employed in proteinuric patients. Aside from histopathological diagnosis, in each patient approximate glomerular filtration, assessed by serum creatinine concentration (mg/dL) and 24 hours' urinary protein excretions (g/d) were noted.

Statistical Analysis

Results were expressed as mean values ± standard deviations (means ± SD).

RESULTS

We analyzed histopathological diagnoses in 82 patients suffering from T2DM, in whom kidney biopsy was performed to evaluate the pathogenesis of proteinuria and/or significant impairment of glomerular filtration.

Diabetic nephropathy was diagnosed in 29 of these patients (35.4%), mean age was 62.52 ± 11.60 years. Twenty-three persons have had advanced, diffuse histopathological changes (79.3%), whereas in 6 cases (20.7%), early DN was diagnosed. Twenty-one patients with DN (72.4%) have had nephrotic proteinuria, exceeding 3.5 g/24 h. Proteinuria and serum creatinine in patients with DN have been presented in Table 1.

In 51 histopathological evaluations of kidney biopsy specimens, obtained from T2DM patients, a diagnosis of NDKD was established (62.2% of all cases reported in this study). The mean age of these patients was 64.62 ± 8.21 years.

MAIN POINTS

- The standard diagnostic approach to proteinuric patients with diabetes mellitus has not included kidney biopsy.
- Our analysis revealed histopathologic features of diabetic nephropathy in only 36.7% of proteinuric diabetic patients (n = 82), whereas in 62.2% of them, a pathological diagnosis of glomerulopathy was established.
- The most common types of glomerular diseases discovered in these subjects were membranoproliferative glomerulopathy (23.8%) and focal segmental glomerulosclerosis (22.2%).
- In the majority of these patients (64.2%), heavy nephrotic proteinuria was found.
- Kidney biopsy is justified in proteinuric patients with type 2 diabetes mellitus, since conclusions from the histopathological assessment may significantly contribute to the management of their glomerular disease.

Table 1. Proteinuria and Serum Creatinine in Patients with Diabetic Nephropathy		
	Advanced	Early
Diabetic nephropathy		
Number of diagnoses	23	6
Proteinuria (mean ± SD, g/24 h)	6.06 ± 1.12	2.9 ± 1.18
Serum creatinine (mean ± SD, mg/dL)	1.69 ± 0.35	1.12 ± 0.45
SD, standard deviation.		

Thirty-four of them have had nephrotic range proteinuria (66.7%) and histopathological diagnoses in these patients included focal segmental glomerulosclerosis (FSGS) in 17 cases (33.3%), primary membranoproliferative glomerulopathy in 10 persons (19.6%), mesangial proliferative non-immunoglobulin A (IgA) nephropathy in 4 cases (7.8%), rapidly progressive glomerulonephritis with extracapillary proliferation in 5 patients (9.8%), IgA nephropathy in 4 cases (7.8%), antineutrophilic cytoplasmic antibody (ANCA)-positive vasculitis in 3 persons (5.8%), membranous nephropathy in 3 patients (5.8%), amyloidosis in 3 patients (5.8%), and minimal change disease in 2 persons (3.9%).

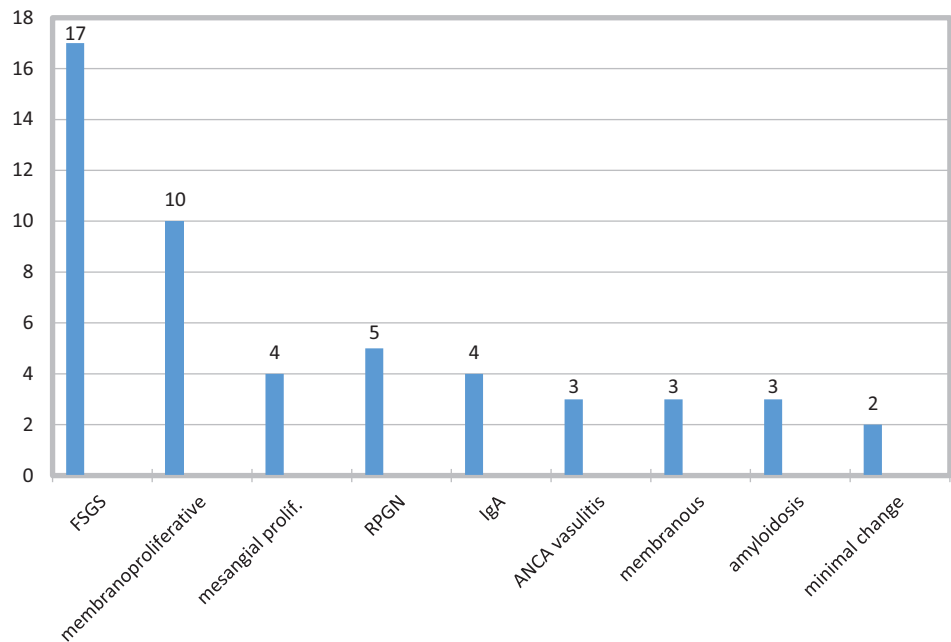
In 2 cases from all 82 patient specimens, the exact type of glomerular disease has not been established in histopathological evaluations of kidney biopsy specimens.

These data have been presented in Figure 1 and Table 2. The diagnosis of non-IgA mesangial proliferative glomerulonephritis was based on histopathological findings of marked mesangial proliferation without any immunoglobulin deposition in the mesangium. Secondary glomerulopathies with or without mesangial proliferation were ruled out on the basis of clinical data, specifically the course of the disease, identification of possible comorbidities, and histopathological evaluation.

DISCUSSION

Most patients with T2DM do not require kidney biopsy to establish diagnosis of DN. It is usually based upon persistently high albumin excretion, duration of diabetes over 10 years, and presence of retinopathy.<sup>4</sup> Nevertheless, a retrospective analysis of 233 patients has demonstrated that 52.3% of them have had evidence of NDKD.<sup>5</sup>

In our study, NDKD was diagnosed in 51 of 82 proteinuric patients with T2DM—62.2%, whereas DN was found in only 29 of these cases (35.4%). It is noteworthy, that in both groups, T2DM and NDKD, a heavy, nephrotic proteinuria was found (T2DM 71.4% of patients and NDKD—64.2%); hence, a degree of urinary protein loss could not be regarded as a sole criterion, qualifying diabetic patients for biopsy to differentiate DN from NDKD.



**Figure 1.** Histological types of 51 nondiabetic glomerulopathies diagnosed in 82 diabetic patients with proteinuria.

In a recent meta-analysis of 40 studies by Tong et al.<sup>6</sup> it has been documented that the NDKD accounted for 58.7% of all proteinuric patients with T2DM. Pure DN was diagnosed in 41.3% of study subjects, comparable to our results (36.7%). Nonetheless, Tong et al.<sup>6</sup> have reported yet another pattern of kidney biopsy findings in subjects with T2DM and proteinuria: co-existence of DN and NDKD features in approximately 18% of all histopathological diagnoses, a subgroup, not identified in our study.

The FSGS was the most prevalent among primary glomerular diseases (33.3%), and it was followed in the frequency of occurrence by the membranoproliferative disease, accounting for 19.6% of all cases. The high prevalence of these 2 primary glomerular diseases in patients with NDKD may be surprising, but a dominant position of FSGS has been reported in some geographical areas (North America<sup>7</sup>). In fact, FSGS is listed among the 2 most frequent glomerulopathies in the general population in Europe, IgA nephropathy ranking first and FSGS the second: 22.1% and 17.9%, respectively.<sup>8</sup> On the other hand, a decreased nephron count due to ischemic nephropathy, secondary to atherosclerosis, could have been responsible for some FSGS cases, seen in our patients.

Table 2. Systemic Diseases with Glomerular Involvement in 51 Patients with Nondiabetic Nephropathy	
Disease	Number of Patients
ANCA-positive vasculitis	3
Amyloidosis	3
ANCA, antineutrophilic cytoplasmic antibody.	

The majority of patients in both nondiabetic and DN groups were found to have significant nephrotic proteinuria: 66.7% and 71.4%, respectively, thus meeting general indications for kidney biopsy. Proteinuria in DN is not regarded as a sole indication for biopsy, nevertheless, since the prevalence of NDKD in T2DM is high, reaching 79% of patients subjected to kidney biopsy,<sup>5</sup> and in our hands, this figure was 62.2%; it is justified to assume that histopathological evaluation is mandatory for appropriate management of proteinuric subjects with T2DM. Yet another reason for performing a percutaneous kidney biopsy in diabetic patients is that it can help predicting clinical course of DN since the severity of glomerular lesions in T2DM is associated with progressive loss of glomerular filtration rate (GFR) in these subjects.<sup>9</sup>

Limitations of this article consist of a lack of detailed clinical data, as well as a description of the course and outcome of nephropathies. However, this report was aimed at the identification of a problem of NDKD in T2DM and an outline of its clinical consequences, instead of a detailed analysis.

**CONCLUSION**

We conclude from this report that indications for kidney biopsy must always be strongly considered in proteinuric subjects with T2DM since the evaluation of histopathological results may enable personalized management of kidney disease in these patients.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Voivodship Specialty Hospital in Wrocław University (Date: February 15, 2019, Decision No: 2/2019).

**Informed Consent:** Written informed consent was obtained from every patient who participated in this study.

**Peer-review:** Externally peer-reviewed.

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