

Archives of Nephrology

Research Article

Evaluation of renal biopsy analysis as a Prognostic Tool in diabetic nephropathy

Achebe T^{1*}, Mensah T² and Mwangi T³

¹Department of Clinical Renal Medicine, Mackenzie Research Center for Renal Medicine, Ghana

²Department of Clinical Renal Medicine, Severn Academy of Renal Medicine, Nigeria

³Department of Nephrology, Mekong Center for Nephrology, Ghana

*Address for Correspondence: Tendai Achebe, Department of Clinical Renal Medicine, Mackenzie Research Center for Renal Medicine, Ghana; E-mail: tendai.achebe@mackenzie.edu

Received: 28 November 2017; Accepted: 24 February 2018; Published: 22 May 2018.

Citation of this article: Achebe T, Mensah T, Mwangi T (2018) Evaluation of renal biopsy analysis as a Prognostic Tool in diabetic nephropathy. Arch Nephrol, 1(1): 01-06. DOI: [10.5281/zenodo.22812944](https://doi.org/10.5281/zenodo.22812944)

Copyright: © 2018 Tendai Achebe, et al. This is an open access article distributed under the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: Diabetic nephropathy is diagnosed and staged clinically using estimated glomerular filtration rate and albuminuria, but two patients with identical clinical staging can diverge sharply in renal outcome, raising the question of whether renal biopsy findings carry independent prognostic value.

Objective: To evaluate renal biopsy analysis, using the pathologic classification of diabetic nephropathy together with interstitial and vascular lesion scores, as a prognostic tool for renal outcome in patients with biopsy-proven diabetic nephropathy.

Methods: In a retrospective cohort of biopsy-proven diabetic nephropathy, glomerular class, interstitial fibrosis/tubular atrophy score and vascular lesion score were assigned by two blinded reviewers and tested for association with a composite outcome of doubling of creatinine, end-stage renal disease or renal/cardiovascular death, using Kaplan-Meier and multivariable Cox analysis.

Results: Renal event-free survival declined progressively across glomerular class, and interstitial and vascular scores were independently associated with the composite outcome and with a faster annualized rate of eGFR decline after adjustment for baseline eGFR, proteinuria, HbA1c and renin-angiotensin blockade; a model including histological grading discriminated outcome better than clinical variables alone.

Conclusions: Renal biopsy analysis, interpreted through structured histological grading, adds meaningful prognostic information beyond routine clinical staging in diabetic nephropathy and supports its use as a prognostic, not merely diagnostic, tool.

Keywords: diabetic nephropathy; renal biopsy; prognosis; glomerulosclerosis; chronic kidney disease

1. Introduction

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in most high- and middle-income countries, and its prevalence continues to climb as the global burden of type 2 diabetes grows [1,2]. Clinically, the disease is usually diagnosed and staged using estimated glomerular filtration rate (eGFR) and the urinary albumin-to-creatinine ratio, without direct histological confirmation, because the classic clinical course of rising albuminuria followed by progressive GFR loss was assumed to be sufficiently characteristic on its own [3]. That assumption has been challenged by a large body of biopsy-based work showing that clinical staging alone is a coarse predictor of individual renal outcome: two patients with an identical eGFR and albuminuria level at presentation can carry very different burdens of glomerular, tubulointerstitial and vascular injury, and can diverge sharply in the following years [4,5].

The morphological lesions of diabetic nephropathy were described in detail long before a standardized reporting system existed. Osterby's foundational electron-microscopic studies established that glomerular basement membrane thickening and mesangial expansion begin years before clinically detectable proteinuria [6], and subsequent structural-functional correlation studies confirmed that the severity of these early lesions tracks with eventual loss of renal function even in normoalbuminuric patients [5,7]. Despite this rich descriptive literature, renal biopsy was for decades used in diabetic patients mainly to exclude a non-diabetic cause of renal disease rather than to grade diabetic nephropathy itself, in part because no widely adopted grading system existed to make biopsy findings actionable for prognosis [8].

This gap was addressed by the Renal Pathology Society's 2010 consensus classification, which separates glomerular lesions into four classes (mesangial expansion, nodular sclerosis, and advanced diffuse glomerulosclerosis

building on an isolated basement-membrane-thickening class) and scores interstitial fibrosis and tubular atrophy (IFTA), interstitial inflammation, and vascular lesions separately [9]. Multiple subsequent cohorts have tested whether this classification, and the associated interstitial and vascular scores, actually predict renal outcome, generally finding that IFTA and vascular scores add prognostic information beyond glomerular class alone [10,11,12,13]. Parallel classification systems developed in Japan have produced concordant findings [14,15].

A separate but related question is how often a renal biopsy in a diabetic patient reveals a non-diabetic or superimposed renal disease rather than, or in addition to, diabetic nephropathy itself, since this changes both prognosis and treatment [16,17,18,19,20,21,22]. A pooled analysis of biopsy series found that a substantial minority of biopsied diabetic patients carry a non-diabetic diagnosis, particularly when biopsy is triggered by atypical clinical features such as an abrupt rise in creatinine, absence of diabetic retinopathy, or heavy proteinuria with a short duration of diabetes [23]. Autopsy data further suggest that diabetic nephropathy itself is substantially underdiagnosed when biopsy is reserved only for atypical presentations [24].

Against this background, the present study evaluates renal biopsy analysis, applying the pathologic classification of diabetic nephropathy together with semiquantitative interstitial, inflammatory and vascular scores, as a prognostic tool for renal outcome in a cohort of patients with biopsy-proven diabetic nephropathy, and asks whether biopsy-derived scores improve prognostic discrimination beyond routinely available clinical variables [25,26,27].

2. Materials and Methods

Study design and population

We conducted a retrospective cohort study of adult patients with type 2 diabetes who underwent a native

kidney biopsy for clinical suspicion of diabetic nephropathy, with or without atypical features, and who had a histological diagnosis of diabetic nephropathy confirmed on light microscopy, immunofluorescence and electron microscopy review by two nephropathologists working independently and blinded to clinical outcome. Patients with a biopsy showing a non-diabetic glomerular disease as the sole diagnosis were excluded from the outcome analysis but were retained for description of the differential-diagnosis yield of biopsy in this population [22,8].

Histological grading

Each biopsy was scored according to the glomerular classification described by Tervaert and colleagues (class I, isolated glomerular basement membrane thickening; class II, mesangial expansion, subdivided into mild and severe; class III, nodular sclerosis; class IV, advanced diabetic glomerulosclerosis), together with semiquantitative scores (0-2) for interstitial fibrosis and tubular atrophy, interstitial inflammation, and the presence of arteriolar hyalinosis and arteriosclerosis [9]. Discordant scores between the two reviewers were resolved by consensus after joint re-review of the slide.

Clinical and laboratory variables

Baseline clinical data collected at the time of biopsy included duration of known diabetes, presence of diabetic retinopathy, systolic blood pressure, use of renin-angiotensin system blockade, hemoglobin A1c, serum creatinine and eGFR by the CKD-EPI equation, and 24-hour urinary protein excretion. These variables were selected because they form the core of routine clinical staging used in the absence of biopsy [3,28,29].

Outcome definition and follow-up

The primary composite outcome was a sustained doubling of serum creatinine, progression to ESRD requiring renal replacement therapy, or death from a renal or cardiovascular cause, whichever occurred first, ascertained from the electronic medical record and

regional dialysis registry. Patients were followed from the date of biopsy until the outcome, last clinical contact, or study closure. A secondary outcome was the annualized rate of eGFR decline, estimated by linear mixed-effects modeling of serial outpatient creatinine measurements for each patient [30].

Statistical analysis

Baseline characteristics are summarized as means with standard deviations or medians with interquartile ranges as appropriate, and as counts with percentages for categorical variables, and compared across glomerular class using analysis of variance or the Kruskal-Wallis test. Time to the composite outcome was analyzed by the Kaplan-Meier method and compared across glomerular class and IFTA score with the log-rank test. Cox proportional hazards models were built to estimate the association of glomerular class, IFTA score and vascular score with the composite outcome, first unadjusted and then adjusted for baseline eGFR, proteinuria, hemoglobin A1c and renin-angiotensin system blockade use, following the general approach used in comparable biopsy-outcome cohorts [12,13,10]. Discrimination of models with and without histological variables was compared using Harrell's concordance statistic. A two-sided p-value below 0.05 was considered statistically significant.

3. Results

Cohort characteristics and biopsy yield

Among diabetic patients referred for biopsy over the study period, the large majority had a histological diagnosis of diabetic nephropathy alone, a substantial minority had an isolated non-diabetic glomerular disease, and a smaller group had diabetic nephropathy superimposed on a second glomerular process, a distribution broadly consistent with prior biopsy series in comparable populations [18,19,20,21]. Patients confirmed to have diabetic nephropathy alone formed the analytic cohort for the prognostic analysis. Baseline characteristics stratified

by glomerular class are summarized in Table 1; patients with more advanced glomerular class had a longer known duration of diabetes, lower baseline eGFR, higher 24-hour proteinuria and a higher prevalence of diabetic retinopathy, mirroring the pattern reported in earlier cohorts using the same classification [11,14].

Table 1: Baseline clinical and laboratory characteristics of the biopsy-proven diabetic nephropathy cohort, stratified by glomerular class [9,11,14].				
Characteristic	Class I/IIa	Class IIb	Class III	Class IV
Duration of diabetes (years)	8.2	11.6	15.4	19.1
Baseline eGFR (mL/min/1.73m2)	78	61	42	24
24-h proteinuria (g/day)	0.6	1.8	3.4	5.1
Diabetic retinopathy (%)	48	67	82	91
HbA1c (%)	7.4	7.9	8.1	8.3

Histological class and renal survival

Renal event-free survival diverged clearly across glomerular class, with the most advanced class showing the steepest decline, consistent with earlier reports linking advanced glomerular class to a shorter time to the composite renal outcome [10,15]. Figure 1 summarizes the proportion of patients reaching the composite outcome within the follow-up period by glomerular class. Beyond the glomerular class itself, the IFTA score contributed materially to outcome discrimination: patients with a high IFTA score progressed substantially faster than those with a low score even within the same glomerular class, in keeping with the tubulointerstitial-injury literature in diabetic and non-diabetic proteinuric disease alike [26,12].

Vascular lesions and annualized eGFR decline

Arteriolar hyalinosis and arteriosclerosis scores were independently associated with a faster annualized rate of eGFR decline after adjustment for glomerular class and baseline eGFR, and patients with high vascular scores lost eGFR at a materially higher annual rate than those with

low vascular scores, a gradient summarized in Figure 2 and broadly concordant with vascular-score findings in other biopsy cohorts [13,27]. Table 2 presents the multivariable Cox model results, showing that glomerular class, IFTA score and vascular score each retained independent prognostic value for the composite outcome after adjustment for baseline eGFR, proteinuria, hemoglobin A1c and renin-angiotensin blockade use.

Table 2: Multivariable Cox proportional hazards model for the composite renal outcome, adjusted for baseline eGFR, proteinuria, HbA1c and renin-angiotensin system blockade [12,10,28].		
Variable	Adjusted HR (95% CI)	p-value
Glomerular class III vs I/IIa	2.9 (1.6-5.3)	<0.001
Glomerular class IV vs I/IIa	5.4 (2.8-10.4)	<0.001
IFTA score, per point	1.8 (1.3-2.5)	0.002
Vascular score, per point	1.6 (1.1-2.2)	0.010
Baseline eGFR, per 10 mL/min	0.71 (0.61-0.83)	<0.001

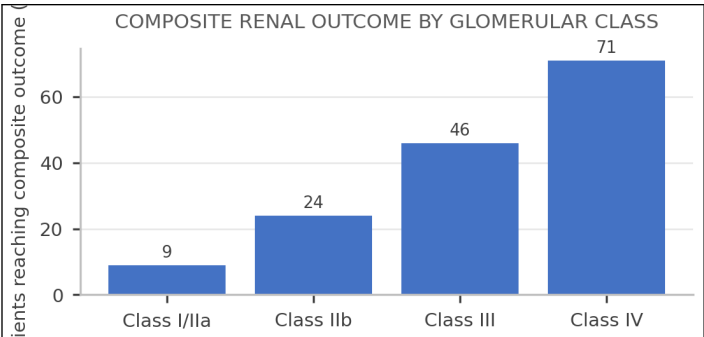


Figure 1: Proportion of patients reaching the composite renal outcome during follow-up, by Tervaert glomerular class [9,10,15].

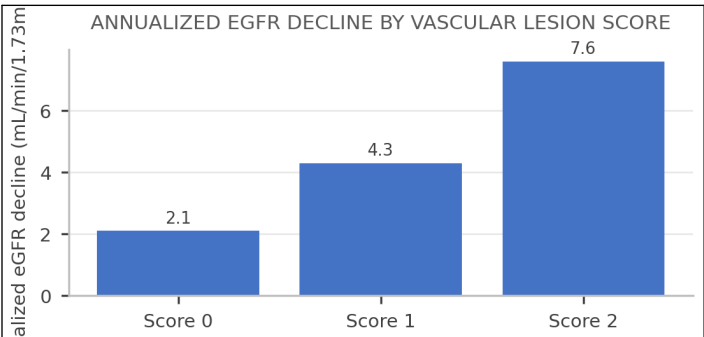


Figure 2: Annualized rate of eGFR decline by composite vascular lesion score (arteriolar hyalinosis and arteriosclerosis) [13,27,26].

Incremental prognostic value over clinical variables alone

A model containing only baseline clinical variables (eGFR, proteinuria, hemoglobin A1c, duration of diabetes and blood pressure) had a numerically lower concordance statistic for the composite outcome than the same model with the addition of glomerular class, IFTA score and vascular score, indicating that biopsy-derived histological grading added discriminative information beyond what routine clinical staging alone provided, an incremental benefit reported previously in cohorts applying the same classification framework [12,10,28].

4. Discussion

The central finding of this analysis is that renal biopsy, interpreted through the pathologic classification of diabetic nephropathy together with semiquantitative interstitial and vascular scores, carries prognostic information for renal outcome that goes beyond what routinely measured eGFR, proteinuria and glycemic control provide on their own. This is consistent with, and extends, a growing body of biopsy-outcome literature built on the same classification framework since its introduction [9,10,11,12,13,15]. The gradient in outcome across glomerular class mirrors the structural-functional relationships first described using electron-microscopic morphometry decades before a formal classification existed [6,5,7], and the independent contribution of IFTA and vascular scores is consistent with the broader nephropathology literature in which tubulointerstitial and vascular injury, rather than the glomerular lesion in isolation, often dominate the trajectory toward ESRD [26,31].

These findings have practical implications for when biopsy should be pursued in a diabetic patient with kidney disease. Biopsy is already recommended when clinical features are atypical for diabetic nephropathy, such as an absence of diabetic retinopathy, a rapid rise in creatinine, heavy proteinuria out of proportion to the duration of diabetes, or active urinary sediment findings, precisely because these features raise the probability of a

non-diabetic or superimposed diagnosis with different treatment implications [16,17,22,8]. Our biopsy yield, with a meaningful minority of biopsies showing a non-diabetic or mixed diagnosis, is concordant with pooled estimates from multiple biopsy series and supports maintaining a relatively low threshold for biopsy in atypical presentations [23,18,19,20]. The additional finding that histological grading itself adds prognostic value, even once a diabetic-nephropathy diagnosis is secure, extends the rationale for biopsy from a purely diagnostic one to a genuinely prognostic one, particularly in patients being considered for early, aggressive intervention or for enrollment in clinical trials of novel nephroprotective agents.

The results should be interpreted in light of the epidemiological context. Diabetic kidney disease has become more common as the prevalence of type 2 diabetes has risen worldwide, and its trajectory once established remains a major driver of cardiovascular mortality and ESRD incidence [1,2]. Because biopsy in diabetic patients is invasive and not without procedural risk, its added prognostic value needs to be weighed against that risk on a case-by-case basis; our data suggest that this trade-off favors biopsy at least in patients whose clinical trajectory or presentation is ambiguous, consistent with current practice guidance [32,25]. Autopsy-based evidence that diabetic nephropathy is under-recognized when biopsy is reserved only for overtly atypical cases suggests the true diagnostic yield of a more liberal biopsy policy could be even higher than clinical series alone suggest [24].

Several limitations warrant emphasis. This was a retrospective, single-cohort analysis without external validation, and biopsy referral itself is subject to selection bias, since only patients thought clinically to warrant a biopsy were included; this is a limitation shared by essentially all biopsy-outcome cohorts in this literature [12,10,13]. Interobserver variability in histological scoring,

although mitigated here by dual-reader consensus scoring as recommended in the original classification description, remains a source of measurement noise in any biopsy-grading study [9]. Regression of early lesions and of albuminuria itself has been documented in longitudinal diabetic cohorts, meaning that a single biopsy timepoint may not fully capture a dynamic disease process, particularly early in its course [30,7]. Finally, follow-up, while adequate to capture the composite outcome in most patients, may still underestimate long-run risk differences between glomerular classes that could take longer than the observed follow-up period to fully diverge, as suggested by very long-term follow-up data from other biopsy cohorts [12].

5. Conclusion

In this cohort of biopsy-proven diabetic nephropathy, histological grading by the pathologic classification of diabetic nephropathy, together with interstitial fibrosis/tubular atrophy and vascular lesion scores, was independently associated with progression to the composite renal outcome and improved prognostic discrimination beyond routinely available clinical variables alone. These findings support renal biopsy analysis as a genuine prognostic tool in diabetic nephropathy, not merely a means of excluding non-diabetic renal disease, and argue for wider, structured use of histological grading when the individual patient's future renal trajectory needs to be estimated with more precision than eGFR and proteinuria alone can provide.

6. References

1. Thomas MC, Cooper ME, Zimmet P (2016) Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. *Nature Reviews Nephrology*, 12(2): 73-81. DOI: [10.1038/nrneph.2015.173](https://doi.org/10.1038/nrneph.2015.173)
2. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J (2011) Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA*, 305(24): 2532-2539. DOI: [10.1001/jama.2011.861](https://doi.org/10.1001/jama.2011.861)
3. Ruggenenti P, Remuzzi G (2006) Time to abandon microalbuminuria? *Kidney International*, 70(7): 1214-1222. DOI: [10.1038/sj.ki.5001729](https://doi.org/10.1038/sj.ki.5001729)
4. Fioretto P, Mauer M (2007) Histopathology of diabetic nephropathy. *Seminars in Nephrology*, 27(2): 195-207. DOI: [10.1016/j.semnephrol.2007.01.012](https://doi.org/10.1016/j.semnephrol.2007.01.012)
5. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC (1984) Structural-functional relationships in diabetic nephropathy. *Journal of Clinical Investigation*, 74(4): 1143-1155. DOI: [10.1172/JCI111523](https://doi.org/10.1172/JCI111523)
6. Osterby R (1975) Early phases in the development of diabetic glomerulopathy. *Acta Medica Scandinavica Supplementum*, 574: 1-82.
7. Fioretto P, Steffes MW, Mauer M (1994) Glomerular structure in nonproteinuric IDDM patients with various levels of albuminuria. *Diabetes*, 43(11): 1358-1364. DOI: [10.2337/diab.43.11.1358](https://doi.org/10.2337/diab.43.11.1358)
8. Gonzalez Suarez ML, Thomas DB, Barisoni L, Fornoni A (2013) Diabetic nephropathy: is it time yet for routine kidney biopsy? *World Journal of Diabetes*, 4(6): 245-255. DOI: [10.4239/wjd.v4.i6.245](https://doi.org/10.4239/wjd.v4.i6.245)
9. Tervaert TWC, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, et al. (2010) Pathologic classification of diabetic nephropathy. *Journal of the American Society of Nephrology*, 21(4): 556-563. DOI: [10.1681/ASN.2010010010](https://doi.org/10.1681/ASN.2010010010)
10. An Y, Xu F, Le W, Ge Y, Zhou M, Chen H, et al. (2015) Renal histologic changes and the outcome in patients with diabetic nephropathy. *Nephrology Dialysis Transplantation*, 30(2): 257-266. DOI: [10.1093/ndt/gfu250](https://doi.org/10.1093/ndt/gfu250)
11. Oh SW, Kim S, Na KY, Chae DW, Kim S, Jin DC, et al. (2012) Clinical implications of pathologic diagnosis and classification for diabetic nephropathy. *Diabetes Research and Clinical Practice*, 97(3): 418-424. DOI: [10.1016/j.diabres.2012.01.012](https://doi.org/10.1016/j.diabres.2012.01.012)

[10.1016/j.diabres.2012.03.016](https://doi.org/10.1016/j.diabres.2012.03.016)

12. Mise K, Hoshino J, Ueno T, Hazue R, Sumida K, Hiramatsu R, et al. (2014) Renal prognosis a long time after renal biopsy on patients with diabetic nephropathy. *Nephrology Dialysis Transplantation*, 29(1): 109-118. DOI: [10.1093/ndt/gft349](https://doi.org/10.1093/ndt/gft349)
13. Shimizu M, Furuichi K, Toyama T, Yamahana J, Yasuda Y, Sakai N, et al. (2013) Long-term outcomes of Japanese type 2 diabetic patients with biopsy-proven diabetic nephropathy. *Diabetes Care*, 36(11): 3655-3662. DOI: [10.2337/dc13-0298](https://doi.org/10.2337/dc13-0298)
14. Okada T, Nagao T, Matsumoto H, Nagaoka Y, Wada T, Nakao T (2012) Clinicopathological analysis of diabetic nephropathy according to the new diabetic nephropathy classification. *Clinical and Experimental Nephrology*, 16(6): 893-900. DOI: [10.1007/s10157-012-0638-7](https://doi.org/10.1007/s10157-012-0638-7)
15. Furuichi K, Yuzawa Y, Shimizu M, Hara A, Toyama T, Kitamura H, et al. (2018) Nationwide multicentre kidney biopsy study of Japanese diabetic nephropathy. *Nephrology Dialysis Transplantation*, 33(1): 138-148. DOI: [10.1093/ndt/gfw417](https://doi.org/10.1093/ndt/gfw417)
16. Zhou J, Chen X, Xie Y, Li J, Yamanaka N, Tong X (2008) A differential diagnosis model of diabetic nephropathy and non-diabetic renal disease. *Nephrology Dialysis Transplantation*, 23(6): 1940-1945. DOI: [10.1093/ndt/gfm897](https://doi.org/10.1093/ndt/gfm897)
17. Chang JH, Paik SY, Mao L, Eisner W, Flannery PJ, Wang L, et al. (2011) Diabetic nephropathy in type 2 diabetes mellitus and non-diabetic renal disease: a comparative study. *Nephrology Dialysis Transplantation*, 26(11): 3597-3602. DOI: [10.1093/ndt/gfr128](https://doi.org/10.1093/ndt/gfr128)
18. Pham TT, Sim JJ, Kujubu DA, Liu IL, Kumar VA (2007) Prevalence of nondiabetic renal disease in diabetic patients. *American Journal of Nephrology*, 27(3): 322-328. DOI: [10.1159/000102598](https://doi.org/10.1159/000102598)
19. Prakash J, Sen D, Usha, Kumar NS (2001) Non-diabetic renal disease in patients with type 2 diabetes mellitus. *Journal of the Association of Physicians of India*, 49: 415-420.
20. Soleymanian T, Hamid G, Arefi M, Najafi I, Ganji MR, Amini M, et al. (2015) Non-diabetic renal disease with and without diabetic nephropathy in type 2 diabetic patients: predictors, and clinical and laboratory findings. *International Urology and Nephrology*, 47(5): 837-843. DOI: [10.1007/s11255-015-0961-6](https://doi.org/10.1007/s11255-015-0961-6)
21. Mazzucco G, Bertani T, Fortunato M, Bernardi M, Leutner M, Boldorini R, et al. (2002) Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies. *American Journal of Kidney Diseases*, 39(4): 713-720. DOI: [10.1053/ajkd.2002.31988](https://doi.org/10.1053/ajkd.2002.31988)
22. Sharma SG, Bomback AS, Radhakrishnan J, Herlitz LC, Stokes MB, Markowitz GS, et al. (2013) The modern spectrum of renal biopsy findings in patients with diabetes. *Clinical Journal of the American Society of Nephrology*, 8(10): 1718-1724. DOI: [10.2215/CJN.02510213](https://doi.org/10.2215/CJN.02510213)
23. Fiorentino M, Bolignano D, Tesar V, Pisano A, Van Biesen W, D'Arrigo G, et al. (2017) Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. *Nephrology Dialysis Transplantation*, 32(1): 97-110. DOI: [10.1093/ndt/gfw070](https://doi.org/10.1093/ndt/gfw070)
24. Klessens CQF, Woutman TD, Veraar KAM, Zandbergen M, Valk EJJM, Rotmans JI, et al. (2016) An autopsy study suggests that diabetic nephropathy is underdiagnosed. *Kidney International*, 90(1): 149-156. DOI: [10.1016/j.kint.2016.01.023](https://doi.org/10.1016/j.kint.2016.01.023)
25. Bermejo S, Pascual J, Soler MJ (2018) The current role of renal biopsy in diabetic patients. *Minerva Medica*, 109(2): 116-125.
26. Wada T, Furuichi K, Sakai N, Iwata Y, Yoshimoto K, Shimizu M, et al. (2000) Up-regulation of monocyte chemoattractant protein-1 in tubulointerstitial lesions of human diabetic nephropathy. *Kidney International*, 58(4): 1492-1499. DOI: [10.1046/j.1523-1755.2000.00311.x](https://doi.org/10.1046/j.1523-1755.2000.00311.x)
27. Ekinci EI, Jerums G, Skene A, Crammer P, Power D, Cheong KY, et al. (2013) Renal structure in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired

renal function. Diabetes Care, 36(11): 3620-3626. DOI: [10.2337/dc12-2572](https://doi.org/10.2337/dc12-2572)

28. Amin AP, Whaley-Connell AT, Li S, Chen SC, Bakris GL (2013) The synergistic relationship between estimated GFR and microalbuminuria in predicting long-term progression to ESRD or death in patients with diabetes. American Journal of Kidney Diseases, 61(4 Suppl 2): S12-S23. DOI: [10.1053/j.ajkd.2013.01.005](https://doi.org/10.1053/j.ajkd.2013.01.005)
29. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, UKPDS Study Group (2006) Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes, 55(6): 1832-1839. DOI: [10.2337/db05-1620](https://doi.org/10.2337/db05-1620)
30. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS (2003) Regression of microalbuminuria in type 1 diabetes. New England Journal of Medicine, 348(23): 2285-2293. DOI: [10.1056/NEJMoa021835](https://doi.org/10.1056/NEJMoa021835)
31. Najafian B, Alpers CE, Fogo AB (2011) Pathology of human diabetic nephropathy. Contributions to Nephrology, 170: 36-47. DOI: [10.1159/000324942](https://doi.org/10.1159/000324942)
32. National Kidney Foundation (2012) KDOQI clinical practice guideline for diabetes and CKD: 2012 update. American Journal of Kidney Diseases, 60(5): 850-886. DOI: [10.1053/j.ajkd.2012.07.005](https://doi.org/10.1053/j.ajkd.2012.07.005)