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Renal biopsy in patients with diabetes: Yesterday, today, and tomorrow

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Diabetic nephropathy (DN) is the most common cause of chronic kidney disease worldwide, occurring in 30%–40% of individuals with diabetes in the United States [1–3], and the number of affected patients continues to rise. DN is classically defined by progressive proteinuria with worsening renal function and reduced glomerular filtration rate (GFR) [2–7], and many patients are clinically diagnosed with DN without histologic confirmation by renal biopsy. These individuals tend to have a long-standing history of diabetes and frequently have evidence of concomitant diabetic retinopathy and/or neuropathy. However, some patients with diabetes and renal dysfunction may present earlier in the disease course or with atypical clinical features such as hematuria, an abrupt increase in proteinuria, or acute kidney injury. Additionally, an increasing number of patients with non-proteinuric diabetic kidney disease (DKD), characterized by declining renal function in the absence of associated albuminuria, have been recognized over the last several years, and the true prevalence of DKD is likely underestimated. In this setting, it can be challenging to determine which patients may have underlying non-diabetic kidney disease (NDKD) for which renal biopsy may be of substantial benefit. In the present editorial, we briefly review the role of renal biopsy in the management of patients with diabetes, as well as some of the more recent investigations into potential digital and molecular methods of evaluating and diagnosing DKD.

1. Historical view of kidney pathology and current renal biopsy practice in diabetes

Since Kimmelstiel and Wilson first described the association of specific glomerular lesions with diabetes in 1936 [8], numerous studies have sought to characterize the types of kidney disease occurring in patients with diabetes. DN has a varied histologic appearance, but characteristically presents with diffuse thickening of glomerular basement membranes (GBMs) and mesangial expansion. Importantly, GBM thickening is an early finding in DN, and may precede the development of clinical microalbuminuria [9, 10]. Basement membranes continue to thicken as the disease progresses, with a subsequent increase in mesangial matrix material. Mesangial expansion may at first be mild before developing the more characteristic nodular appearance (Kimmelstiel-Wilson nodules), which often shows areas of mesangiolysis with associated microaneurysm formation of glomerular capillary loops [11]. Global and segmental glomerulosclerosis is frequently found later in the disease course, with associated variable and sometimes extensive podocyte foot process effacement by electron microscopy [9, 11]. Other common morphologic findings include hyalinosis of glomeruli and Bowman capsule (capsular drops), afferent and efferent arteriolar hyalinosis, interstitial scarring with associated inflammation and eosinophils, and diffuse linear accentuation of glomerular and tubular basement membranes with polyclonal IgG and albumin by immunofluorescence microscopy [3, 9, 11–13]. Additionally, patients with non-proteinuric DKD have been shown to have more extensive arteriosclerosis and tubulointerstitial scarring in relation to the severity of glomerular lesions [5, 7]. In an attempt to more reliably stratify the histologic lesions of DN, a system was developed in 2010 which categorizes glomerular lesions into four classes based on their severity [14]. While this scheme has produced good interobserver agreement with regard to the glomerular lesions of DN, a wide variety of lesions may still be encountered within each class, and tubulointerstitial involvement is evaluated separately and excluded from the overall grade. Therefore, although useful for characterizing the glomerular lesions of DN, the clinical and predictive utility of this classification scheme has yet to be established [2, 3, 14].

There has been extensive investigation into the types of kidney disease occurring in patients with diabetes over the last several decades. Although limited by selection bias toward patients with atypical clinical presentations, studies have identified NDKD in anywhere from 12% to 81% of biopsies [15], with more recent retrospective studies from large centers reporting NDKD as the primary diagnosis in up to 50% of the biopsies from patients with diabetes [9, 12]. Similar to the general

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population, the most common NDKD diagnoses include focal segmental glomerulosclerosis (FSGS), IgA nephropathy, hypertensive nephrosclerosis, and acute tubular injury, with hypertensive nephrosclerosis, acute tubular injury, and secondary FSGS frequently accompanying a diagnosis of DN. Indications for biopsy in diabetic patients often include hematuria, active urine sediment, and acute kidney injury, or a rapid decline in renal function, positive serologic studies, monoclonal gammopathy with renal dysfunction, and nephrotic syndrome [1, 12, 15]. Although considered atypical in DN, hematuria has not been shown to reliably identify NDKD, and may be present in around a third of cases of DN [15]. One study found the presence of monoclonal gammopathy to be more often associated with NDKD; however, only about 25% of those cases showed evidence of paraprotein-related disease on renal biopsy [12], and it was not found to be predictive of NDKD in a later study [9]. While a long-standing history of diabetes (>10 years) was predictive of underlying DN [12], the presence of diabetic retinopathy as a predictor of DN is debatable [9, 16]. Interestingly, nephrotic-range proteinuria has been shown to be more common in patients with DN compared to NDKD in multiple studies [9, 12, 15]. While these studies do not separate patients who experience an abrupt onset from those with progressive proteinuria, this finding argues against using isolated severe proteinuria as the sole indication for renal biopsy in patients with diabetes.

Although progressive proteinuria is classically associated with DN, studies over the past several years found that between 25% and 50% of patients with diabetes and CKD did not have associated microalbuminuria [2–6], somewhat limiting the use of albuminuria as a marker of DN. These patients were shown to have a lower risk of CKD progression [7] and differing associations with cardiovascular events and mortality than patients with typical DN [4]. Clinically, patients with non-proteinuric DKD may have lower rates of retinopathy [4], with other possible risk factors including older age and female sex [5, 7]. Renal biopsy in non-proteinuric DKD tends to demonstrate heterogeneous histopathologic changes with more extensive interstitial and vascular involvement compared to classic DN, as previously mentioned. These features suggest that non-proteinuric DKD may have a different pathogenesis, with greater contribution from arteriosclerosis and tubulointerstitial scarring rather than microvascular injury [4, 5, 7]. Another important and often underrecognized form of DKD occurs in the post-transplantation setting in patients without a history of diabetes. Although the rate of post-transplant diabetes has improved with modern immunosuppression, between 10% and 30% of solid organ transplant patients may go on to develop diabetes [17]. DKD in this setting is thought to be related to a combination of insulin resistance and β-cell dysfunction; however, more research is needed to better understand the pathophysiology and prognostic significance of post-transplantation DKD. Ultimately, due to the widely variable clinical presentation of DKD, renal biopsy is likely underutilized in patients with diabetes based on the current biopsy indications [1, 12, 15].

2. Kidney biopsy in diabetes in the era of precision medicine

Besides traditional histopathologic evaluation of renal biopsies, investigators have recently begun to explore the use of digital pathology and machine learning as means of assisting pathologists in the classification of histopathologic lesions in DN [18]. While significant work remains, computational methods have been shown to be able to reliably detect and classify glomerular structures and lesions in DN through machine learning. In the future, utilization of artificial intelligence by pathologists may allow for more extensive and detailed histopathologic evaluation of renal biopsies, leading to a better understanding of the prognostic significance of the morphologic and structural changes seen with DN and improved diagnostic precision in affected patients.

Another area of interest is the underlying molecular alterations associated with the development and progression of DKD. Genetic susceptibility for DKD was first observed in families several decades ago and has been subsequently well-documented [19]. Over the past decade, a number of studies have been performed on renal biopsy tissue in an attempt to better understand the molecular pathways involved with DN in the hopes of identifying potential biomarkers which could ultimately augment or partially replace renal biopsy in patients with diabetes. For example, one study using single cell RNA sequencing identified altered expression of genes related to processes such as ion transport and angiogenesis in patients with DN [20]. Additionally, several genome-wide association studies (GWAS) have been conducted on renal biopsy tissue from diabetic patients of different backgrounds and ethnicities, and have identified several genetic variants and single nucleotide polymorphisms (SNPs) associated with DN. These SNPs are associated with numerous kidney functions, including GBMs and inflammatory pathways [19, 21, 22]; however, the precise mechanisms through which these genetic alterations are involved with DN has yet to be elucidated. Another area of study has dealt with microRNAs (miRNAs), which are key regulators of gene expression and govern the expression of >60% of protein-coding genes [23, 24]. A number of miRNAs have been identified in association with various pathways and processes related to DN. For instance, MiR-192 and miR-216a are involved in the transforming growth factor-β (TGF-β) signaling pathway, which plays a role in DN by contributing to interstitial fibrosis and extracellular matrix accumulation [24]. The expression of miRNA-21, which is involved in processes such as collagen gene expression and podocyte injury, was altered in DN [23, 24]. In addition to possible usefulness as biomarkers, targeting miRNAs may eventually provide a new therapeutic option in DN. Several small molecules have already been shown to inhibit or induce miRNAs in some cancer cells and other disease models and could potentially have future utility in the treatment of DN [24].

Likewise, proteomic analysis of renal tissue also has the potential to discover disease-specific proteins and biomarkers. In a recent study, proteomic analysis of laser microdissected glomeruli from formalin-fixed, paraffin-embedded renal tissue in patients with DN showed overexpression of the extracellular matrix protein, nephronectin [25]. Associated with a number of renal and urologic diseases, the role of nephronectin in the development of diabetic glomerulosclerosis is intriguing and requires further studies. Lastly, in addition to tissue-based biomarkers, some circulating and urinary proteins have also been suggested as prognostic indicators in DKD. These include circulating tumor necrosis factor receptors 1/2 and IL-15RA, which are inflammatory markers associated with progression to end-stage renal disease [26], and urinary kidney injury molecule-1 (KIM-1) an epithelial transmembrane glycoprotein expressed from the renal proximal tubular cells after injury [27]. Although the use of molecular testing and digital pathology shows promise for the evaluation and prognostication of patients with DKD, further studies are necessary before these modalities can be ready for use in daily practice.

There are currently nearly half-a-billion people with diabetes worldwide, and the number of affected individuals is expected to continue to increase [28]. A significant percentage of these patients will develop some degree of renal dysfunction related to diabetes; however, DKD has a highly variable clinical presentation, and differentiating these patients from those with underlying NDKD based solely on clinical and laboratory findings can be difficult if not impossible. Although molecular testing and artificial intelligence may someday supplement or reduce the utilization of renal biopsy in patients with diabetes, there is currently no established role for these studies in daily clinical practice. Thus, with between 33%–50% of biopsied patients receiving a primary diagnosis of NDKD and up to 20% of patients having a diagnosis favoring therapy beyond standard treatment for DN [9], histopathologic diagnosis continues to be the most reliable method for differentiating DN from NDKD and providing valuable prognostic information. Suffice it to say, renal biopsy will remain an important tool in the management of patients with diabetes and renal dysfunction for the foreseeable future.

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Conflict of Interest

Xinjin Zhou is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and his research groups.

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