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REVIEW

# The kidney in diabetes: dynamic pathways of injury and repair. The Camillo Golgi Lecture 2007

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**Abstract** Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD). The natural history of diabetic nephropathy has changed over the last decades, as a consequence of better metabolic and blood pressure management. Thus, it may now be possible to delay or halt the progression towards ESRD in patients with overt diabetic nephropathy, and the decline of renal function is not always inexorable and unavoidable. Also, the rate of progression from microalbuminuria to overt nephropathy is much lower than originally estimated in the early 80s. Furthermore, there is now evidence that it is possible, in humans, to obtain reversal of the established lesions of diabetic nephropathy. This review focuses on the contribution of kidney biopsy studies to the understanding of the pathogenesis and natural history of diabetic nephropathy and the identification of patients at high risk of progression to ESRD. The classic lesions of diabetic nephropathy and the well-established structural–functional relationships in type 1 diabetes will be briefly summarised and the renal lesions leading to renal dysfunction in type 2 diabetes will be described. The relevance of these biopsy studies to diabetic nephropathy pathogenesis will be outlined. Finally, the evidence and the possible significance of reversibility of diabetic renal lesions will be discussed, as well as future directions for research in this field.

**Keywords** Morphometric analysis · Renal structure · Type 1 diabetes · Type 2 diabetes

**Abbreviations**

| | |
|---|---|
| DN | diabetic nephropathy |
| ESRD | end-stage renal disease |
| GBM | glomerular basement membrane |
| PTA | pancreas transplant alone |
| TBM | tubular basement membrane |

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## The changing natural history of diabetic nephropathy

Large long-term clinical trials have demonstrated that improved blood glucose [1, 2] and blood pressure [3–5] control (e.g. through use of renin–angiotensin blockers) slows the development and/or progression of diabetic nephropathy (DN). Indeed, as a result of these improvements the natural history of DN has changed over the last decades. Thus, it may now be possible to delay or halt progression towards end-stage renal disease (ESRD) in patients with overt DN [3–5]. This contrasts with the concept that by the time patients have overt nephropathy, the decline in renal function is inevitable.

The natural history of the disease at earlier stages may also have changed. In the early 1980s the risk of progression

to overt proteinuria (AER >200 μg/min) in microalbuminuric (AER 20–200 μg/min) type 1 diabetic patients was estimated to be about 80% over a decade [6–8]. More recently, prospective studies have demonstrated that the percentage of type 1 diabetic patients with microalbuminuria who progress to proteinuria over 10 years is only about 30% [9–13]. This apparent decrease may be due to an overestimation of risk in earlier studies, improved prognosis as a result of advancements in treatment, or a combination of the two. In fact, the concept that a substantial proportion of microalbuminuric patients spontaneously regress to normoalbuminuria is now well established [9–13]. In type 2 diabetes, the progression rate from microalbuminuria to proteinuria is similar (around 30% in 10 years) [14]. In the Steno-2 study, during a 7.8 year follow-up of 151 microalbuminuric type 2 diabetic patients, 31% progressed to proteinuria, 31% regressed to normoalbuminuria and 38% remained microalbuminuric [15]. It is interesting that the rate of GFR decline was much lower in patients who regressed to normoalbuminuria (2.3 ml $min^{-1}$ $year^{-1}$) than in patients who progressed to proteinuria (5.4 ml $min^{-1}$ $year^{-1}$), suggesting that regression to normoalbuminuria is associated with preservation of renal function [15].

We have demonstrated that prolonged euglycaemia, achieved through pancreas transplantation, leads to reversal of established lesions of DN in patients with type 1 diabetes [16]. These findings contradict the long-held belief that the lesions of DN are irreversible, and further contribute to the changing natural history of DN.

## Pathways of injury

### Renal lesions in type 1 diabetes

In type 1 diabetic patients, glomerulopathy is characterised by thickening of the glomerular basement membrane (GBM) and mesangial expansion, leading to a progressive reduction in the filtration surface of the glomerulus [17, 18] (Fig. 1). Although the most important structural changes occur in the glomeruli [17, 18], concomitantly and approximately in proportion to the degree of glomerulopathy, the arterioles [19], tubules [20] and interstitium [21] also develop morphological lesions. Thus, these extraglomerular lesions usually become severe only in the presence of advanced glomerulopathy, typically in patients with overt proteinuria and/or decreasing GFR.

The first changes that can be measured are thickening of the GBM and tubular basement membrane (TBM) [22]. Within few years after the onset of diabetes, afferent and efferent arteriolar hyalinosis can also be noted. Mesangial expansion can be detected in some patients as early as 5–7 years after diabetes onset [17], and when diffuse and

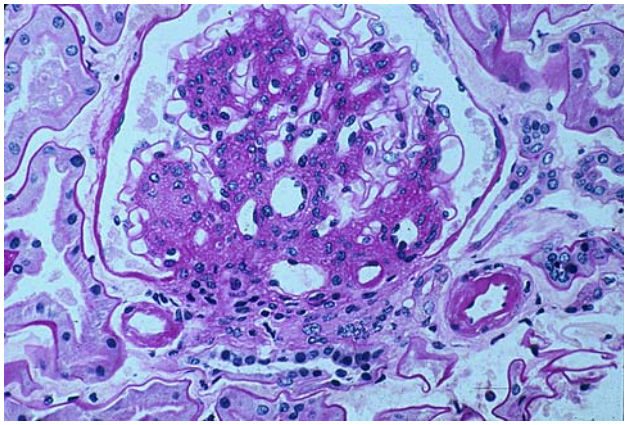

**Fig. 1** Glomerulus from a type 1 diabetic patient with diffuse and nodular mesangial expansion, glomerular basement membrane (GBM) thickening and afferent and efferent arteriolar hyalinosis (periodic acid–Schiff stain). Reprinted from [18]

generalised is termed diffuse diabetic glomerulosclerosis. Nodular glomerulosclerosis consists of areas of marked mesangial expansion forming large, round, fibrillar mesangial zones with palisading of mesangial nuclei (Kimmelstiel–Wilson nodules). Additional abnormalities include global glomerular sclerosis [23] and interstitial expansion [21]. More recently, we reported that the onset of proteinuria is associated with the development of new glomerular lesions, specifically, widespread abnormalities of the junction of the proximal tubule with the glomerulus, which ultimately lead to separation of the glomerulus from its tubule (atubular glomeruli) and, thus, loss of glomerular function [24, 25].

Studies of the relationships between structural and functional parameters have demonstrated that the critical lesion of DN, leading to progressive loss of renal function, is mesangial expansion [17]. However, in advanced stages of the disease, interstitial, tubular and glomerulo-tubular junction injuries drive the progression towards ESRD [24, 25].

We have studied glomerular structure in a large cohort of long-standing type 1 diabetic patients with AER levels ranging from normoalbuminuria to high levels of microalbuminuria [26]. All variables of glomerulopathy were, on average, abnormal in the normoalbuminuric group, although approximately half of the patients had normal structure. No patients with an AER of >30 μg/min had normal glomerular structure [26]. Interestingly, in several normoalbuminuric patients, the severity of glomerulopathy overlapped with that in patients with high levels of microalbuminuria [26]. It is tempting to hypothesise that normoalbuminuric patients with more advanced lesions have an increased risk of progressing to microalbuminuria and proteinuria, and our published [27] and unpublished data support this view. In contrast, patients with an increased AER but glomerular parameters near the normal range are more likely to revert to normoalbuminuria. Although an increase in AER in the microalbuminuric range is usually the first clinical expres-

sion of DN, in some long-term type 1 diabetic patients this is instead a reduced GFR [28]. We have observed that a subset of long-term normoalbuminuric type 1 diabetic patients, most often women with diabetic retinopathy and/or hypertension, may still be normoalbuminuric despite having a reduced GFR (<90 ml $min^{-1}$ 1.73 $m^{-2}$) [28]. These patients have more advanced glomerulopathy lesions than those with normoalbuminuria and a normal GFR. These findings have been confirmed, especially in type 2 diabetes, where this condition has been termed 'normoalbuminuric renal insufficiency' [29].

## Renal lesions in type 2 diabetes

The majority of studies on renal structure in diabetes have been performed in patients with type 1 diabetes, and assumptions have been made that renal pathology in type 2 diabetes is the same as in type 1 diabetes. However, renal lesions in type 2 diabetes are much more complex. First, in contrast with type 1 diabetes, the prevalence of non-diabetic renal lesions in proteinuric type 2 diabetic patients has been reported to be high (approximately 30%) [30, 31]. However, a much lower occurrence of non-diabetic renal disease (12%) was reported in a series of 33 proteinuric patients [32]. This broad variability is likely to be related to different criteria adopted from clinic to clinic for kidney biopsy indications [33]. We performed a large number of research kidney biopsies in patients with type 2 diabetes, and found that <10% of the proteinuric patients had non-diabetic renal diseases. However, we have described marked heterogeneity in renal structure in these patients [34]. Indeed, only a minority had histopathological patterns resembling those typically present in type 1 diabetes. The remainder had very mild or absent diabetic glomerulopathy with or without tubulo-interstitial, arteriolar and global glomerulosclerosis changes. Based on these findings we proposed a classification system that included three major categories [34]:

1. Category I: Normal or near-normal renal structure. These patients (35% of those with microalbuminuria and 10% of those with proteinuria) had biopsies that were normal or showed very mild lesions (Fig. 2a).
2. Category II: Typical diabetic nephropathology. These patients (30% of those with microalbuminuria and 55% of those with proteinuria) had established diabetic lesions with an approximately balanced severity of glomerular, tubulo-interstitial and arteriolar changes. This picture is typical of that seen in type 1 diabetes (Fig. 1).
3. Category III: Atypical patterns of renal injury. These patients (35% of those with microalbuminuria and proteinuria) had relatively mild glomerular diabetic changes considering the disproportionately severe changes in other renal structures, including tubular atrophy, TBM thickening and reduplication, interstitial fibrosis (Fig. 2b), advanced glomerular arteriolar hyalinosis commonly associated with atherosclerosis of larger vessels, and global glomerular sclerosis. These findings have been confirmed by electron microscopy studies, as discussed below.

Thus, the renal lesions leading to renal dysfunction differ in type 2 and type 1 diabetes. The tubulo-interstitial and vascular changes are likely to be related not only to hyperglycaemia, but also to ageing, atherosclerosis and systemic hypertension, which often pre-dates the onset of type 2 diabetes. However, it is also possible that the heterogeneity in renal structure might reflect the heterogeneous nature of type 2 diabetes itself. Interestingly, patients with 'typical' (Category II) DN lesions had a longer known diabetes duration, worse metabolic control and they all had diabetic retinopathy (50% background, 50% proliferative). In contrast, none of the patients in Categories I and III had proliferative retinopathy, and background retinopathy was observed only in 50% of Category I and 57% of Category III patients [34]. This suggests the possibility that the different underlying pathophysiological mechanisms responsible for type 2 diabetes in these groups of patients may also underlie different renal and retinal pathophysiological mechanisms or responses.

The heterogeneity in renal structure in patients with type 2 diabetes has important clinical implications, in that patients with different patterns of renal injury may respond differently to various therapeutic agents. Indeed, we have observed that this heterogeneity in renal structure affects renal prognosis, as patients with typical DN (Category II) have a faster GFR decline than patients with very mild glomerulopathy, with or without tubulo-interstitial and vascular lesions (Categories I and III) [35]. Extrapolating these findings to the recent natural history data in microalbuminuric type 2 diabetic patients [15], it is tempting to speculate that patients with typical diabetic glomerulopathy (Category II) are more likely to progress to overt nephropathy and experience a faster GFR loss, while patients without glomerulopathy are more likely to regress to normoalbuminuria (Category I, normal renal structure) or to remain microalbuminuric (Category III, tubulo-interstitial and/or vascular lesions) with minimal loss in renal function.

The data on structural–functional relationships in type 2 diabetes based on quantitative morphometric analysis are less abundant. In Japanese type 2 diabetic patients, morphometric measures of diabetic glomerulopathy showed correlations with renal functional parameters similar to those observed in type 1 diabetes [36]. Similar structural–functional relationships have also been reported in 21 white

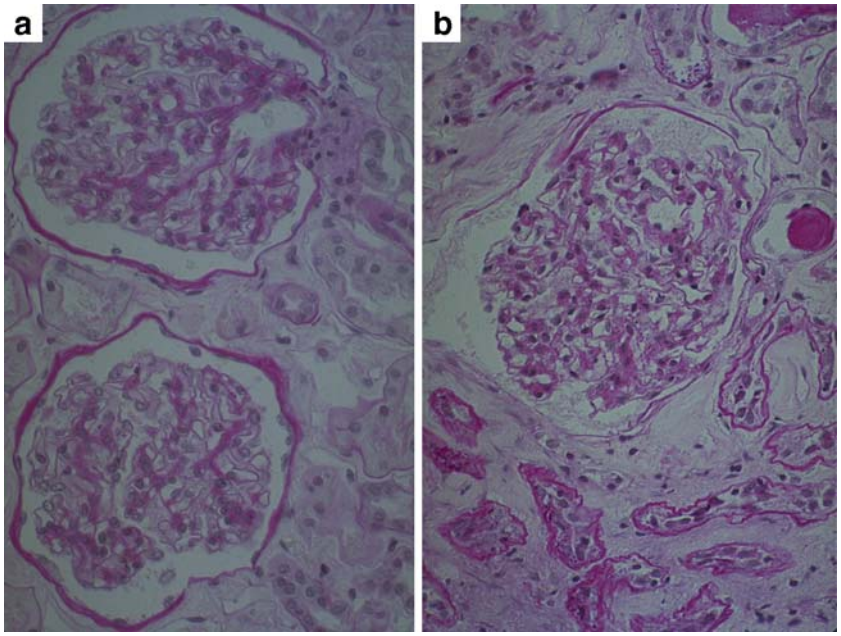


**Fig. 2** Renal biopsies from microalbuminuric type 2 diabetic patients (periodic acid–Schiff stain). **a** Normal glomerular, tubular, interstitial and vascular structures. This would be classified as Category I. **b** Mild mesangial expansion relative to the severity of interstitial fibrosis and tubular atrophy. This would be classified as Category III. Reprinted from [34], with kind permission of Springer Science+Business Media

diabetic individuals with overt nephropathy [37]. In this latter study, creatinine clearance was correlated with both mesangial and interstitial expansion, suggesting an important role of interstitial lesions in determining loss of renal function in patients with advanced DN [37]. These findings differ from those of a previous study [38] on type 2 diabetic patients with overt nephropathy, which reported that, although all glomerular parameters were, on average, abnormal, some patients had normal glomerular structure. In contrast, in type 1 diabetic patients with overt nephropathy, glomerular structure was always severely altered [38]. We have analysed research kidney biopsy samples, obtained from a large group of Italian type 2 diabetic patients, using electron microscopic morphometric analysis, and found that the degree of glomerular structural lesions increased with increasing albuminuria, from normoalbuminuria to proteinuria (P. Fioretto, unpublished data). However, several patients, despite persistent microalbuminuria or proteinuria, had normal glomerular structure. Moreover, compared with type 1 diabetic patients with similar renal function, diabetic glomerulopathy was less advanced in patients with type 2 diabetes. The relationships between renal function and glomerular structural variables were significant, but less precise than in patients with type 1 diabetes. By cluster analysis, we compared the correlations between AER and morphometric measures of glomerular structure in type 1 and type 2 diabetic patients and observed that approximately one-third of type 2 diabetic patients fall outside the cluster for structural–functional relationships (of the individual structural variables) for the type 1 diabetic patients (P. Fioretto, B. Najafian, Department of Laboratory Medicine and Pathology, University of Minnesota, unpublished data). This is because a substantial proportion of type 2 diabetic patients have an increased AER, despite the paucity of diabetic glomerulopathy lesions. These findings largely confirm our initial description, by light microscopy, of heterogeneity in renal structure among patients with type 2 diabetes and an increased AER [34]. Although the prognostic relevance of falling outside the cluster has yet to be fully described, we have reported that the rate of GFR decline was significantly correlated with the severity of diabetic glomerulopathy lesions in a large cohort of type 2 diabetic patients, who underwent precise GFR determinations over a follow-up period of 4 years [35].

Thus, renal lesions different from those typical of diabetic glomerulopathy should be considered when investigating the nature of an abnormal AER in type 2 diabetes. These lesions include changes in the structure of renal tubules, interstitium, arterioles and, within the glomeruli, podocytes.

Pima Indians with type 2 diabetes and proteinuria have fewer podocytes per glomerulus than those without nephropathy [39]. Also, over a 4 year follow-up period, a lower number of podocytes per glomerulus at baseline was the strongest predictor of greater increases in AER and a higher risk of progression to overt nephropathy in microalbuminuric patients [40]. These observations suggest that podocyte loss is important in the progression to overt nephropathy, rather than in its genesis and early development.

In a cohort of 67 type 2 diabetic patients with AER values ranging from normoalbuminuria to proteinuria [41], the density of podocytes per glomerulus was significantly decreased in all diabetic patients compared with controls, and it was lower in microalbuminuric and proteinuric patients than in normoalbuminuric patients. The absolute number of podocytes per glomerulus was also lower in

microalbuminuric and proteinuric patients compared with controls; however, only the density was significantly correlated with AER. In addition, microalbuminuric and proteinuric patients had increased foot process width compared with normoalbuminuric patients, and this was directly related to AER. Decreased density and number of podocytes and increased foot process width have also been described in 16 type 2 diabetic patients with nephropathy (median proteinuria 570 mg/24 h) compared with normal controls [42].

These results suggest that, in white type 2 diabetic patients, changes in podocyte structure and density occur in the early stages of DN and might contribute to increasing albuminuria in these patients. Moreover, podocyte structural changes could in part explain abnormal albuminuria in patients without diabetic glomerulopathy [41]. Podocytes probably have a limited capacity for replication, such that when they are lost they cannot be easily replaced by new cells. Thus, the loss of podocytes, together with the increase in glomerular volume caused by diabetes, necessarily require the residual cells to cover a larger area of GBM. This could cause foot process widening and detachment, resulting in bare GBM areas with consequent proteinuria. Moreover, these areas of detachment could initiate adhesions and be potential starting points for abnormalities in glomerulo-tubular junctions and focal or global glomerular sclerosis.

## Pathways of repair: reversal of diabetic renal injury

The lesions of DN have been considered to be irreversible. If reversal is possible, this should happen during long-term normoglycaemia, which is currently achievable only by pancreas transplantation. This procedure, performed in uraemic patients at the time of renal transplant or, less frequently, after kidney transplant, prevents or slows the development of early diabetic glomerulopathy lesions in the renal allograft [43, 44].

We have studied 13 recipients of pancreas transplantation alone (PTA) and found that, despite 5 years of normoglycaemia, the lesions of DN were unaffected [45]. At 10 years post-PTA, eight patients were available for follow-up studies [16]; at this time, reversal of diabetic glomerular and tubular lesions was obvious in all eight patients [16]. By light microscopy, a remarkable amelioration of glomerular structure was evident, including total disappearance of Kimmelstiel–Wilson nodular lesions (Fig. 3). Thus, GBM and TBM widths and mesangium fractional volume were decreased at the 10 year follow-up, returning to normal values in most patients (Fig. 4). Additional patients have now been studied at 5 and 10 years after PTA, and we can confirm that glomerular lesions remained unchanged at 5 years but showed a clear improvement and healing at 10 years. The worsening of interstitial fibrosis and tubular atrophy observed at 5 years post-PTA (Fig. 5a,b) [46], likely consequent to ciclosporin therapy, was reversed at 10 years post-PTA (Fig. 5c) [47]. We observed remodelling of the tubulo-interstitial lesions in the 10 year vs the 5 year biopsy samples, with decreases in the cortical interstitial fractional volume and the fractional volume of tubules that were atrophic and an overall decrease in renal interstitial fibrillar collagen [47]. These tubulo-interstitial structural improvements might be attributable to prolonged normoglycaemia (probably also in association with the restoration of C-peptide secretion), decreased cyclosporine dose or both. The reasons for the long delay in the reversal of DN lesions are unknown. Nevertheless, the long time necessary for these diabetic lesions to disappear is consistent with their slow rate of development. Regardless of the mechanisms involved, at some point after PTA, glomerular, tubular and interstitial cells changed their behaviour towards extra cellular matrix (ECM) removal and architectural remodelling, demonstrating the remarkable ability of the kidney to recover from injury and heal. The understanding of the molecular and cellular mechanisms involved in these repair processes could provide new directions for the treatment of DN.

Other therapeutic approaches, such as antihypertensive agents, as discussed below, have not been described to lead to amelioration or reversal of diabetic renal lesions.

## Where should we go from here?

Since interventions at later stages of DN may slow but not always prevent progression to ESRD, improved primary prevention strategies are needed. These will require a more complete understanding of the pathogenesis of early diabetic renal injury in addition to improved predictors of DN risk.

We have previously argued that AER levels within the so-called ‘normoalbuminuric’ range, together with currently available risk factors, such as family history, ambulatory blood pressure measurements, retinopathy evaluations, glycaemic and lipid levels, may allow earlier risk profiling than the dichotomisation of patients into the categories of ‘normoalbuminuria’ and ‘microalbuminuria’ [11]. In addition, increased precision of risk prediction would be helpful among microalbuminuric patients. New, more accurate, means of defining early risk would not only help select those patients who would benefit from more aggressive treatment with currently available modalities, but would also likely provide pathogenetic insights leading to new treatment options. Kidney biopsy studies are crucial in the search for new early and specific predictors, such as blood or urinary biomarkers. Indeed, early markers/predictors can

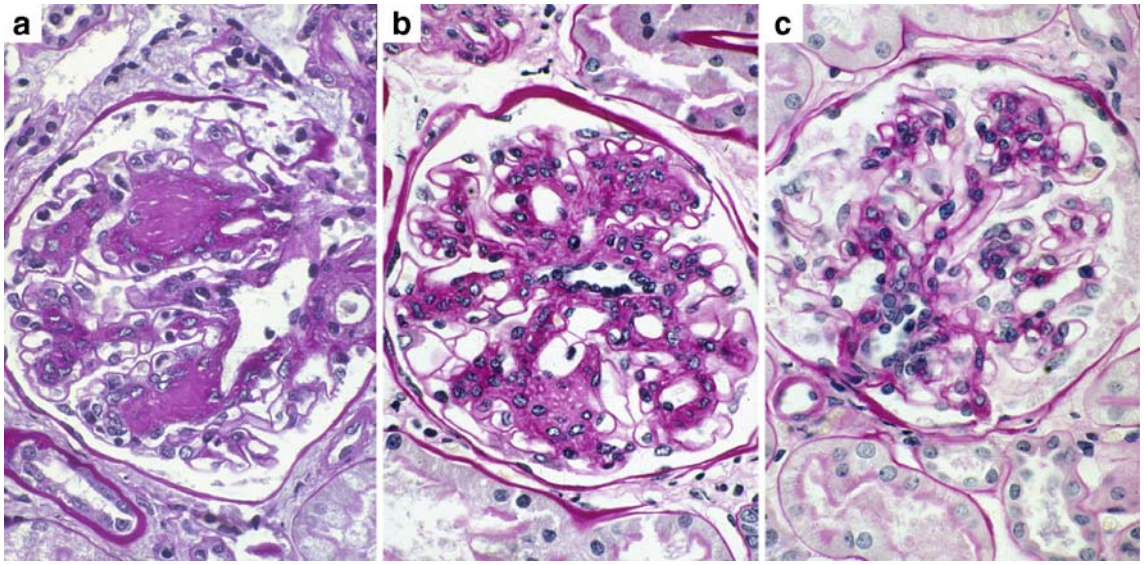


**Fig. 3** **a** Diffuse and nodular mesangial expansion in a type 1 diabetic patient prior to pancreas transplant alone (PTA). **b** Persistence of diffuse and nodular mesangial expansion 5 years after successful PTA in the same patient shown in **a**. **c** Marked reduction of mesangial expansion 10 years after successful PTA in the same patient shown in panels **a** and **b**. All sections stained with periodic acid–Schiff stain. Reprinted with permission from [16]. Copyright © 1998 Massachusetts Medical Society. All rights reserved

be identified using overt proteinuria as the endpoint, but this would require decades of follow-up. Alternatively, the emerging new markers can be related to renal structural lesions known to predict long-term renal outcome, and this would require kidney biopsies. This approach to early identification of high risk patients would be especially helpful in type 2 diabetes, given the heterogeneity of renal lesions underlying abnormal AER. As discussed above, the degree of glomerulopathy predicts GFR decline; thus, the identification of non-invasive indicators of the different renal lesions would have important prognostic significance. Natural history studies of type 1 and type 2 diabetic patients with no discernable clinical renal disease have paved the way for research in this direction. Moreover, the availability of markers associated with glomerular vs tubulo-interstitial lesions would allow better definition of the phenotype of type 2 diabetic patients for genetic studies and clinical trials.

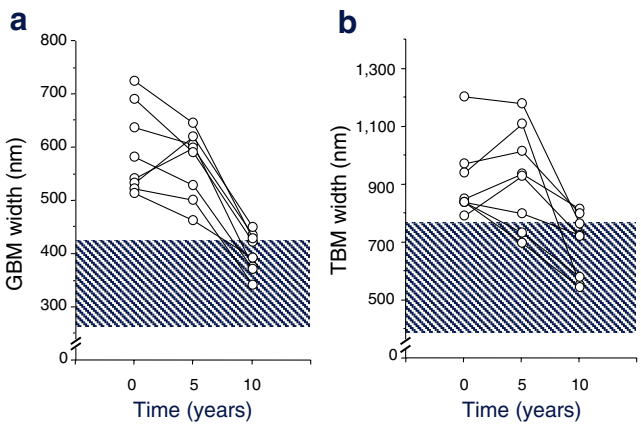


**Fig. 4** Thickness of GBM and TBM at baseline, and 5 and 10 years after PTA. The shaded areas represent the normal ranges obtained in 66 age- and sex-matched normal kidney donors. Data for individual patients are connected by lines. Reprinted with permission from [16]. Copyright © 1998 Massachusetts Medical Society. All rights reserved

Genetic predisposition to DN has been strongly suggested in multiple cross-sectional studies in type 1 [48–50] and type 2 diabetic [51, 52] siblings concordant for diabetes. Importantly, diabetic sibling pairs, known to be concordant for DN risk, are highly concordant for diabetic glomerulopathy lesions [53]. This risk seems to be substantial, in part independent of glycaemia [54]. There are ongoing searches for genetic loci related to DN susceptibility through genomic scanning and candidate gene approaches, although neither approach has yet yielded definitive results [55]. Genetic polymorphisms in candidate genes have been evaluated in several studies; the most extensively studied genes are perhaps those in the renin–angiotensin system. Several other genes have been studied, and a couple have been given special attention lately. A leucine repeat in the gene encoding carnosinase was associated with DN in both type 1 and type 2 diabetic patients [56, 57]. Multiple variations in the gene encoding superoxide dismutase 1 were significantly associated with persistent microalbuminuria and severe nephropathy in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study [58]. In the Family Investigation of Nephropathy and Diabetes (FIND) study, genome-wide scan demonstrated multiple chromosomal regions linked to estimated GFR in multiethnic families ascertained by a proband with DN [59]. In our view, the research renal biopsy is an important tool in genetic studies that allows precise definition of the renal phenotype; this is particularly relevant for patients with type 2 diabetes, as discussed above.

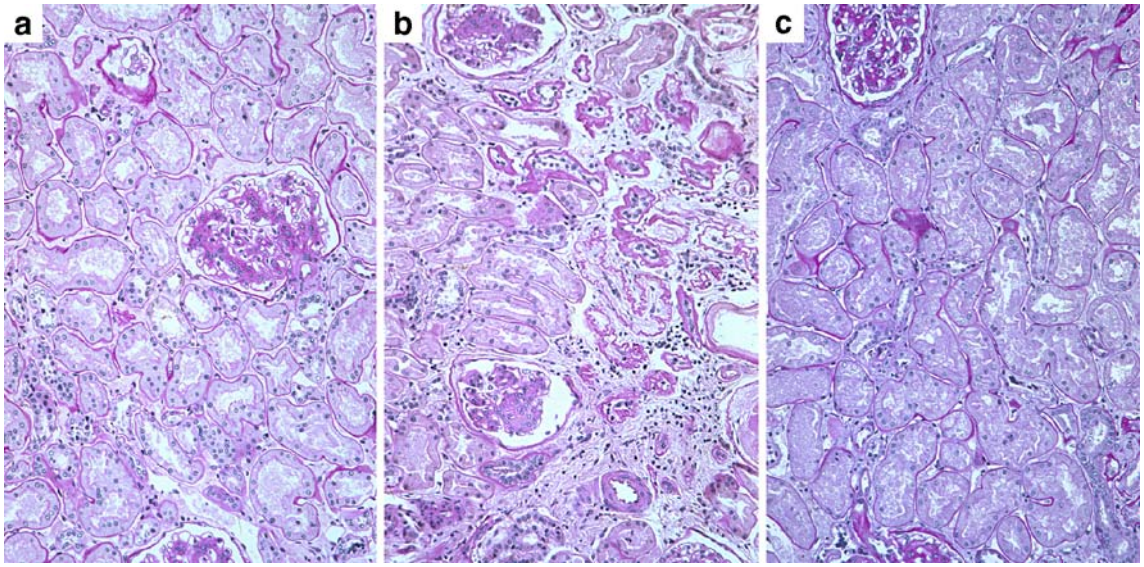


**Fig. 5** **a** Moderate to advanced diabetic glomerulopathy with near normal tubules and interstitium in this type 1 diabetic patient prior to PTA. **b** Persistence of the diabetic glomerulopathy changes and de novo interstitial fibrosis and tubular atrophy 5 years after PTA in the same patient shown in panel **a**. Reprinted from [47]. **c** Near normalisation of glomerular structure, marked resolution of interstitial fibrosis and reabsorption of atrophic tubules, 10 years after PTA in the same patient shown in panels **a** and **b**. All sections stained with periodic acid–Schiff stain

Clinical trials have clearly demonstrated that antihypertensive therapy, especially with RAS blockade, is effective in slowing progression of DN [3–5]. Also, multifactorial intervention strongly reduces the risk of progressing to overt nephropathy and ESRD [60]

Dual blockade, using ACE inhibitors and angiotensin receptor blockers, and the use of anti-aldosterone agents and renin blockers are promising treatment options. However, to date, only short-term studies on the effects on AER are available. Studies of the effect of RAS blockade on renal structure so far have been largely underpowered (small numbers, short duration of follow-up). Thus, in a small group of 54 normotensive (BP <150/90 mmHg) type 1 diabetic patients with an AER of between 30 and 1500 μg/min, ACE inhibitor therapy (enalapril) for 3 years did not affect glomerular or interstitial structures [61]. Indeed, there was no change over this time interval in any structural parameter in the enalapril, nifedipine or placebo groups. Another study compared renal structure before and after 38 months of treatment with enalapril or metoprolol in 13 type 1 diabetic patients with microalbuminuria [62], reporting no change over time in either group. In 19 type 2 diabetic patients, 2 years of treatment with perindopril prevented the progression of interstitial fibrosis compared with controls [63], without affecting glomerular structure. Thus, RAS blockade, effective in postponing ESRD, has not so far been shown to have a favourable effect on renal structure. In particular, in the studies above, there was no evidence of an improvement or reversal of DN lesions.

A wide variety of possible treatments that could prevent DN injury or speed repair have been suggested from rodent studies, including inhibition of NADPH oxidase assembly by apocynin [64], administration of the AGE crosslink breaker, alagebrium [65], and many others, beyond the scope of this review. However, extrapolation from rodent studies to humans is fraught with difficulties, and new drug testing is problematic (see below). For example, protein kinase C inhibition by ruboxistaurin showed some promise in reducing albuminuria and sustaining GFR in proteinuric type 2 diabetic patients after 1 year of treatment [66], but is not currently being actively pursued; an indication of the critical research challenges in this area.

Thus, as clearly demonstrated by the studies performed to date [61–63], clinical trials using renal structure as an endpoint, especially in the early stages of DN, require large numbers and, most importantly, a long follow-up duration (likely 7–10 years). This would require the cooperation of industries and national funding agencies, along with strong commitment from the investigators and patients.

The pancreas transplant studies clearly demonstrated truly remarkable capabilities for renal glomerular and tubulo-interstitial healing and remodelling in the human kidney. One can now envision diabetic glomerulopathy as the expression of a long-standing imbalance between processes of injury and repair. If this is indeed the case, then research, heretofore almost entirely focused on understanding mechanisms of renal injury in diabetes, should broaden its horizons to include studies on repair. Teleologically, the cells of the glomerulus must sense their abnormal ECM environment and architectural distortion and have the cellular mechanisms necessary to engineer ECM removal that exceeds production. This represents scar-free healing

[67], a striking characteristic of early fetal life. As the capability for liver regeneration makes clear [68], there are time-specific variations in regeneration capacity in humans. In addition, the healing capacities may be influenced by the inflammatory responses [69]. Newer high-throughput research tools [67] applied to this area could improve our understanding of healing processes, which may use signalling pathways similar to those involved in the original injury [70]. Thus, subtle manipulations of these injury/repair processes could lead to major benefits in terms of disease prevention and treatment.

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