

## **The kidney in type 2 diabetes: focus on renal structure**

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### **INTRODUCTION**

The renal lesions underlying renal dysfunction are different in type 2 and type 1 diabetes. Renal structure is heterogeneous in type 2 diabetic patients, with only a subset presenting typical diabetic glomerulopathy, as in type 1 diabetes. The remaining patients have more advanced tubulo-interstitial and vascular than glomerular lesions, or normal/near normal renal structure. The clinical manifestations of diabetic nephropathy are significantly related with glomerular structural changes, especially with the degree of mesangial expansion; however these relationships are less precise than in patients with type 1 diabetes. Probably several other important structural changes are involved, including tubular, interstitial and vascular lesions. Indeed, in the last years, changes in the structure and number of podocytes have been demonstrated to be involved in the pathogenesis of diabetic nephropathy; recently is emerging that also proximal tubular structural abnormalities might contribute to increasing albuminuria in type 2 diabetic patients. This review summarizes the renal structural abnormalities and the structural–functional relationships in type 2, compared to type 1, diabetic patients.

### **RENAL LESIONS IN 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. In type 1 diabetic patients, glomerulopathy is characterised by thickening of glomerular basement membrane (GBM) and mesangial expansion, leading to a progressive reduction in the filtration surface of the glomerulus<sup>1,2</sup>. Although the most important structural changes occur in the glomeruli<sup>1,2</sup>, concomitantly the arterioles, tubules and interstitium also develop morphological lesions<sup>3</sup>. These extraglomerular lesions usually become severe only in presence of advanced glomerulopathy, typically in patients with overt proteinuria and/or decreasing glomerular filtration rate (GFR).

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Studies of the relationships between structural and functional parameters have demonstrated that the critical lesion of diabetic nephropathy, leading to progressive loss of renal function, is mesangial expansion<sup>1</sup>. However, in advanced stages of the disease, interstitial, tubular and glomerulo-tubular junction injuries drive the progression towards ESRD<sup>4</sup>. In contrast with type 1 diabetes, in type 2 diabetic patients we have described marked heterogeneity in renal structure. Indeed, only a minority had histopathological patterns resembling those typically present in type 1 diabetes. The remaining 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<sup>4</sup>:

- Category I: normal or near-normal renal structure. These patients (30% of those with microalbuminuria and 10% of those with proteinuria) had biopsies that were normal or showed very mild lesions.
- Category II: typical diabetic nephropathology. These patients (30% of those with microalbuminuria and 50% 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.
- Category III: atypical patterns of renal injury. These patients (40% 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, advanced glomerular arteriolar hyalinosis commonly associated with atherosclerosis of larger vessels, and global glomerular sclerosis.

Thus, the renal lesions leading to renal dysfunction differ in type 2 and type 1 diabetes. It is possible that the heterogeneity in renal structure might reflect the heterogeneous nature of type 2 diabetes itself. Interestingly, all patients with 'typical' (category II) lesions 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<sup>4</sup>. 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. Moreover 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. 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)<sup>5</sup>.

Moreover a significant prevalence of non-diabetic renal lesions in proteinuric type 2 diabetic patients has been reported. Indeed it has been described that a significant proportion of type 2 diabetic patients with nephropathy has a variety of glomerulopathy including minimal change nephropathy, IgA nephropathy, chronic glomerulonephritis and mesangial proliferative glomerulonephritis alone or superimposed to diabetic structural abnormalities.

## STRUCTURAL-FUNCTIONAL RELATIONSHIPS

The data on structural–functional relationships in type 2 diabetes based on quantitative morphometric analysis are less abundant than in type 1 diabetes. 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<sup>6</sup>. Similar structural–functional relationships have also been reported by White et al<sup>7</sup> in a small number of white diabetic individuals with overt nephropathy. 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. These findings differ from those of a previous study by Osterby et al<sup>8</sup> on type 2 diabetic patients with overt nephropathy, in which a great variability in glomerular injury has been reported and the authors outlined that type 2 diabetic patients tended to have less marked glomerular changes than type 1 with similar renal function. We have analysed research kidney biopsy samples, obtained from a large group of type 2 diabetic patients, using electron microscopic morphometric analysis, and found that the degree of glomerular structural lesions increased with increasing albuminuria. However, several patients, despite persistent microalbuminuria or proteinuria, had normal glomerular structure. The relationships between renal function and glomerular structural variables were significant, but less precise than in patients with type 1 diabetes; interestingly 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<sup>9</sup>. 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<sup>10</sup>. 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<sup>11</sup>. These observations suggest that podocyte loss is important in the progression to overt nephropathy, rather than in its genesis and early development. In a large cohort of type 2 diabetic patients with AER values ranging from normoalbuminuria to proteinuria<sup>12</sup>, we described that 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 and inversely 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. 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. 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 requires 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. Recently we also analyzed the proximal tubular basement membrane width (TBM width) and the degree of interstitial expansion [Vv(Int/cortex)] in a group of type 2 diabetic patients. Preliminary, unpublished data suggested that, as in type 1 diabetes, TBM thickening is present in type 2 diabetic patients and probably plays a role in the pathogenesis of AER. Vv(Int/cortex) was not related to renal functional parameters. Different courses of renal function in type 2 diabetic patients are probably related to different patterns of renal structural abnormalities, and these diffe-

rent renal lesions might have different impacts on AER and GFR.

## Conflict of interest

The authors declare they have no conflict of interest.

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