Type 1 Diabetes Mellitus:
The Relationship of Clinical and Renal Structural Changes

By Julia Steinke

Diabetic nephropathy (DN)—the progressive decline in renal function usually accompanied by proteinuria, hypertension, and declining glomerular filtration rate (GFR)—is a major complication of longstanding diabetes. After 15–25 years of diabetes, approximately 25–40 percent of patients with type 1 diabetes mellitus (T1DM) will ultimately develop signs of renal involvement. According to the USRDS database, diabetic nephropathy is the single most important cause of end stage renal disease (ESRD) in the United States, Japan, and Europe. Most importantly, much of the renal injury from diabetes occurs in clinical silence before the majority of symptoms or laboratory findings suggestive of DN become evident.

Early abnormalities such as microalbuminuria or hypertension may occur as early as seven years after onset of diabetes but typically take longer to develop. The first detectable renal structural change is an increase in glomerular basement membrane (GBM) width and is followed by an increase in the fraction of the glomerulus occupied by the mesangium, composed of mesangial matrix and cells (Table 1). GBM width has been found to be one of the earliest changes that occur in patients with T1DM, even prior to the onset of overt clinical signs of renal injury, such as microalbuminuria. GBM widening is not only the earliest and most obvious abnormal finding among renal structural parameters, but the most prevalent abnormal finding among morphometric measures regardless of duration of diabetes (Table 1). On the other hand, there is very little change in the mesangial measures for the first 10–15 years of diabetes duration with a rapid increase thereafter (Figure 1).

The expansion of the mesangium is predominantly due to accumulation of mesangial matrix with less contribution from the mesangial cells. With advanced disease, progressive renal functional loss ensues due to glomerular collapse and sclerosis, and by capillary lumen obliteration resulting from massive mesangial expansion. Interstitial fibrosis and tubular atrophy at these later stages of the disease process may also contribute to functional loss. Other renal lesions include afferent and efferent arteriolar hyalinosis and capsular drops that are virtually pathognomenic of diabetes and have been reported rather early in the disease process. The combined effects of glomerular basement membrane thickening, mesangial expansion, glomerular sclerosis, tubular atrophy, and interstitial fibrosis all contribute to eventual loss of renal function in progressive stages.

The typical clinical course of diabetic nephropathy has been described as the initial onset of microalbuminuria and hypertension with the later development of overt proteinuria and finally decline in renal function. The first clinical signs of renal injury can be expressed by changes within "normal limits" of measurable parameters. For example, subtle increases in blood pressure—within the range of normal detected by 24-hour blood pressure monitoring—often precede the development of microalbuminuria. Further blunting of the normal 10 percent decline, commonly referred to as "dipping," in nocturnal blood pressure becomes more pronounced as microalbuminuria and proteinuria develop. Blood pressure changes may develop in parallel or even precede rises in albumin excretion. Hypertension itself is a promoter of GFR decline in patients with diabetic nephropathy.

Although the prevalence of hypertension in patients with T1DM and normal albumin excretion is no different than that in the general population, it is significantly higher in T1DM patients with either microalbuminuria or overt proteinuria. Higher prevalence of elevated systolic and diastolic blood pressure has even been reported in the adolescent population with T1DM and microalbuminuria compared to age-matched normoalbuminuric patients. However, even subtle increases in nocturnal mean arterial blood pressure, detected with 24-hour ambulatory blood pressure monitoring, in normoalbuminuric T1DM patients are an important indicator of renal structural injury. The current literature certainly supports the use of renin angiotensin blockade in patients with microalbuminuria to slow progression to proteinuria, but there is a lack of support for such treatment in those without any clinical evidence for renal injury such as elevated albumin excretion.

Type 1 diabetes is associated with early and prolonged glomerular hyperfiltration, i.e., a glomerular filtration rate (GFR) above normal limits. The presence of hyperfiltration in young patients with type 1 diabetes has been reported to increase the risk of developing microalbuminuria later on, independent of glycemic control and blood pressure. However, this relationship of GFR and microalbuminuria remains controversial as reduced GFR below the lower limit of normal (<90 mL/min/1.73 m^2) has been reported to be associated with more advanced glomerular lesions despite normal urinary albumin excretion. Therefore, it appears that the reliability of GFR as an indicator of clinically detectable injury without the use of a renal biopsy to compare is debatable.

Morphometry studies have demonstrated the importance of renal biopsy data when clinicians are evaluating microalbuminuria and renal function. It appears that mesangial changes are most closely correlated with renal function. The disproportionate increase in mesangium relative to the expansion in glomerular volume is closely correlated with a decrease in the GBM filtration surface density and thereby is related to a decline in GFR. This mesangial expansion is closely related not only to diminished GFR but to the development of microalbuminuria and hypertension.

Improvement in glycemic control, measured by glycated hemoglobin (HbA1c), in as little as three years has also shown to be correlated with slowed renal injury. The beneficial results of optimal glycemic control clearly have a sustained effect in the decreased incidence of microalbuminuria as well as decreased rates of other microvascular injury, such as retinopathy and neuropathy, as shown in the Diabetes Control and Complications Trial (DCCT) and the follow-up of this study in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. The EDIC study showed that, despite a decreased difference in mean HbA1c between the two treatment groups, there was less progression in urinary albumin excretion in those who had been tightly controlled in the previous DCCT study. Based largely on the results of these studies, aggressive glycemic management has become the cornerstone of recommendations made by the American Diabetes Association.

Multiple studies have shown improved glycemic control can contribute to slowed progression of renal morphological changes. Recently, blood glucose fluctuations have been reported as being an additional factor influencing accelerated rates of renal complications related to diabetes. Emerging data suggest that complications in T1DM may be closely associated with glycemic excursions perhaps through oxidative stress and glycation changes. The influence of glucose control on structure was perhaps best demonstrated by the pivotal report of reversal of GBM width changes back to normal occurring a decade after pancreatic transplantation in T1DM patients. There appears to be no question that better glycemic control is an important element in the prevention and even the resolution of renal injury.

Type 1 diabetes mellitus remains one of the leading causes of ESRD. Patients who develop ESRD from diabetes are at higher risk of mortality and associated microvascular morbidities. There have been tremendous strides in our understanding of the progression of renal disease in type 1 diabetes mellitus as well as the risks that may impact this rate of progression, such as the profound importance of maintaining strict glycemic control. However, there are other considerations such as gender, genetics, and renal hemodynamics that clinicians should also consider when evaluating a young person with diabetes and renal structural changes. We have only begun to understand the multitude of factors that may influence the varying trajectories of renal injury.

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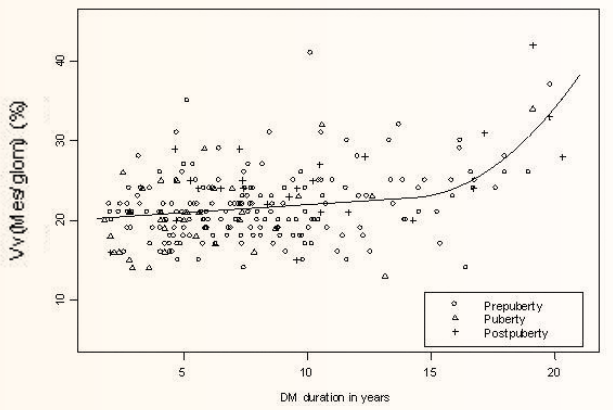
Table 1. Percentage of abnormal morphometric parameters in relation to duration of diabetes

		Duration of type 1 diabetes			
Variable	**Abnormal value***	**2–8 years**	**8–14 years**	**14–20 years**	**All durations**
n		144	74	25	243
GBM (nm)	>445	23	50	68	36
Vv(Mes/glom)	>0.25	10	16	48	16
Vv(MM/glom)	>0.11	15	31	68	25
Vv(MC/glom)	>0.13	3	3	12	4

Duration data are percent. * >95th percentile of normal, nondiabetic control subjects.

Abbreviations: GBM, glomerular basement membrane; Vv(Mes/glom, fraction of the glomerulus occupied by mesangium; Vv(MM/glom), fraction of glomerulus occupied by mesangial matrix; Vv(MC/glom), fraction of glomerulus occupied by mesangial cells [Drummond K, Mauer M. The early natural history of nephropathy in type 1 diabetes: II early renal structural changes in type 1 diabetes. *Diabetes* 2002; 51:1580–1587].

Figure 1. Mesangial fractional volume as a function of disease duration in three subgroups defined by age at onset of type 1 diabetes



Abbreviation: Vv(Mes/glom), morphometry measurement indicating the fraction of glomerulus occupied by the mesangium [Drummond K, et al. Effects of duration and age at onset of type 1 diabetes on preclinical manifestations of nephropathy. *Diabetes* 2003; 52:1818–1824].