Renal Structure and Function in Insulin-Dependent Diabetes Mellitus and Type I Membranoproliferative Glomerulonephritis in Humans

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ABSTRACT

Renal pathological changes of diabetes include thickening of all renal extracellular basement membranes and the mesangial matrix and, to a lesser extent, mesangial cell expansion. Two renal lesions appear critical in diabetic nephropathy. Mesangial expansion out of proportion to the size of the glomerulus is related to proteinuria, hypertension, and declining GFR. Arteriolar hyalinosis is related to global glomerulosclerosis, and both are correlated with the clinical features of nephropathy. By the time renal dysfunction is clinically detectable, these lesions tend to be advanced. Interstitial volume may be increased in insulin-dependent diabetes mellitus, particularly in areas containing sclerotic glomeruli or marked tubular atrophy. Parallel findings were documented for type I membranoproliferative glomerulonephritis in which the increased mesangial volume fraction was related to decreased GFR, increased glomerular permeability to protein, and hypertension. As in diabetes, the cortical interstitial volume fraction is correlated with functional abnormalities in type I membranoproliferative glomerulonephritis. Thus, in both of these chronic glomerular disorders, mesangial expansion and interstitial expansion are associated with disordered renal function. Thus, it is not true that glomerular structural changes correlate poorly with glomerular function. Whether it is the glomerular or interstitial pathology or both that is causally responsible for the dysfunction requires further study.

Key Words: Diabetic nephropathy, membranoproliferative glomerulonephritis, glomerular structure, glomerular function

A variety of pathological lesions of the kidney have been described in diabetes mellitus, which, taken together, present a picture unique to this disorder. Kimmelstiel and Wilson provided the original description of nodular glomerulosclerosis, now known as the Kimmelstiel-Wilson nodule (1). They also described the capsular drop, a collection of hyaline material under the parietal epithelium of Bowman’s capsule (1). Other lesions include diffuse mesangial expansion (diffuse glomerulosclerosis), exudative hyaline lesions within the glomerular capillary walls (fibrin caps), and arteriolar hyalinosis.

Accurate stereological techniques have allowed quantification of the structural changes of diabetic nephropathy (2,3), permitting correlation of these changes with renal function. These studies have been carried out primarily in insulin-dependent diabetes mellitus (IDDM). Light microscopy studies suggest that the pathologic changes of non-insulin-dependent diabetes mellitus (NIDDM) are similar to those of IDDM (4); electron microscopic morphometric studies in these patients confirm that glomerular lesions in NIDDM patients resemble those of IDDM patients (Østerby R, personal communication). It is important to note that about 25% of NIDDM patients with proteinuria have a renal disease other than diabetic nephropathy (5).

GLOMERULAR BASEMENT MEMBRANE

Measurement of the glomerular basement membrane (GBM) width (2) demonstrates thickening in almost all long-standing IDDM patients (6,7). This is measurable after 2 yr of diabetes (6,8) and is usually uniform both within and between glomeruli. The nature of this thickening is not completely understood, but it primarily involves the lamina densa and, at least initially, the so-called "novel chains" of type IV and type VI collagen (9; D. Zhu, M.W. Steffes, Y. Kim, S.M. Mauer, work in progress).

GBM width correlates poorly with mesangial volume fraction and with the functional parameters of
GFR and hypertension (7). However, there is a stronger correlation of GBM width with urinary albumin excretion (UAE) across the broad range from normal UAE to heavy proteinuria.

**MESANGIUM**

Shortly after the onset of IDDM, the fraction of the glomerular tuft occupied by the mesangium is normal, with roughly equal proportions of cells and matrix, as it is in normal subjects (10). After 2 to 3 yr, the matrix and, to a lesser extent, the mesangial cell volume begin to increase (11,12) out of proportion to any increase in glomerular volume. In fact, through all grades of mesangial expansion throughout the natural history of this disorder, the dominant mesangial change is an increase in the relative matrix volume (13). This increase in the mesangial volume fraction [Vv(Mes/gbom)] becomes marked after many years of diabetes in patients progressing to overt nephropathy (7,14).

Mesangial expansion demonstrates important correlations with renal function in diabetic nephropathy (7). There is a strong inverse correlation between Vv(Mes/gbom) and GFR. This probably results from the expanding mesangium compromising the structure of contiguous glomerular capillaries. Vv(Mes/gbom) is inversely related to the peripheral capillary filtration surface density, and filtration surface/gbomerulus has been shown to be directly proportional to GFR (15,16). Virtually all patients with marked mesangial expansion [Vv(Mes/gbom) >37%] have had more than 400 mg of albumin in their urine/24 h; all patients in this earlier study had hypertension (7), although this is not inevitable because one fourth of patients developing overt nephropathy are normotensive (S.M. Mauer et al., work in progress). Thus, marked mesangial expansion is associated with all of the clinical manifestations of diabetic nephropathy. Understanding the nature of the expansion of the mesangial matrix is key to the unraveling of the pathogenesis of diabetic nephropathy. Our preliminary studies (Zhu D et al., work in progress) indicate that the immunohistochemistry of the mesangial matrix is probably similar in IDDM patients with very slow development of lesions compared with that in those with rapid progression. This suggests that the nephropathy risk is related to the rate of matrix accumulation rather than to matrix component alterations.

It is important to discuss the relationship of microalbuminuria to the structural lesions of diabetic nephropathy. Using mesangial expansion as the key structural parameter (17), it was found that patients with long-standing IDDM and entirely normal renal function, as indicated by normal UAE, GFR, and blood pressure, have Vv(Mes/gbom) ranging from normal to levels bordering on those regularly associated with overt nephropathy (0.37) (18). Patients with microalbuminuria, normal GFR, and normal blood pressure (UAE usually <45 mg/24 h or 30 μg/min) have Vv(Mes/gbom) completely overlapping with those whose renal function is entirely normal (15). Those IDDM patients with microalbuminuria and hypertension, decreased GFR, or both (UAE usually >45 mg/24 h or 30 μg/min) have more advanced mesangial expansion (15). Normal UAE does not preclude the presence of important lesions, and microalbuminuria does not necessarily predict structural abnormalities. However, if other manifestations of overt nephropathy are present, then microalbuminuria indicates more advanced structural injury (18). In other words, microalbuminuria in the range regularly "predictive" of the later development of proteinuria is, in fact, a marker of well-established diabetic glomerular pathology and is often associated with subtle abnormalities in other clinical parameters indicative of diabetic nephropathy, including hypertension and declining GFR. Nonetheless, the measurement of UAE in the subproteinuric range is a key parameter to follow in patients with long-standing diabetes.

**GLOMERULAR ARTERIOLES**

Hyaline changes involve both the afferent and efferent glomerular arterioles in diabetes and very occasionally in other conditions (19). This ranges in severity from small amounts of periodic acid-Schiff-positive translucent material under the elastic membrane of the arterioles to virtually complete replacement of the smooth muscle cells of the vessels by this material. Hyaline deposits in these vessel walls, along the parietal layer of Bowman's capsule (capsular drop), and in the glomerular subendothelial space (fibrin cap) all appear to contain the same materials, such as immunoglobulins, fibrinogen, and complement, as well as other plasma proteins (20). The pathogenesis of these lesions is unknown. We have recently found that the more advanced glomerular arteriolar lesions, defined as complete replacement of smooth muscle cells by hyaline, are directly correlated with greater numbers of globally sclerotic glomeruli (21), which are, in turn, inversely correlated with GFR. This suggests that glomerular sclerosis in diabetic nephropathy may derive in part from vascular pathology and may adversely influence renal function. An additional mechanism of glomerular sclerosis in diabetes may be extreme mesangial expansion with consequent capillary closure (14).

**STRUCTURAL FUNCTIONAL CHANGES IN TYPE I MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS**

Glomerular volume is increased in type I membranoproliferative glomerulonephritis (MPGN) (22). The
mesangial volume fraction is increased, and unlike the case in diabetes nephropathy where most of the increase is due to matrix accumulation, in type I MPGN, this increase is largely due to expansion of the cellular compartment of the mesangium. In type I MPGN, as in diabetes, mesangial expansion is inversely related to filtration surface and to GFR. Also, hypertension and proteinuria are directly related to the degree of mesangial expansion and are inversely related to changes in filtration surface. Cortical interstitial volume fraction in MPGN as in diabetes is also correlated with the clinical expression of this disorder (22).

GLOMERULAR STRUCTURE AND LOSS OF FUNCTION

It is our hypothesis that a decreasing filtration surface is "viewed" by the kidney as a decrease in renal mass. Thus, the advanced pathologic changes of diabetes and MPGN, we suggest, stimulate adaptive hemodynamic responses (23) and, perhaps, other forces (24,25), resulting in the disruption of permeslectivity, the production of proteinuria, and the development of hypertension. This hypothesis argues that once the primary lesions of these disorders produce clinically detectable renal dysfunction, then the pathology is already far advanced and the processes leading to the progressive loss of kidney function become substantially independent of the initiating causes and thus similar to those of advanced renal injury in general.

The filtration surface is ultimately determined by the filtration area/glomerulus and the number of glomeruli/individual. Filtration area/glomerulus is inversely proportional to the Vv(Mes/glom) (7.15,22). As the mesangium expands and occupies a greater proportion of the glomerular tuft, the capillary volume must decrease, unless accompanied by expansion of the entire glomerular volume. If accumulation of mesangial material exceeds the ability of the glomerulus to hypertrophy, the capillary loops will ultimately close, resulting in a completely obliterated glomerulus. Thus, mesangial expansion may decrease functioning filtration surface both by decreasing the surface/glomerulus and by decreasing the number of functioning glomeruli. Glomerular number in diabetes may also be decreased by vascular disease, as discussed above (21) and as suggested by Horlyck et al. (26).

Finally, the role of interstitial volume expansion in adversely influencing renal function in diabetes and MPGN deserves more detailed studies. Although studies have shown inverse correlations between GFR and interstitial expansion in diabetes (7,27), an independent role for interstitial pathology in the evolution of glomerulopathies has not been established. Our ongoing studies in diabetes indicate that the increased interstitial volume that is associated with renal dysfunction in diabetes occurs in contiguity with lesions of global glomerular sclerosis and marked tubular atrophy. Thus, interstitial expansion in diabetes may be a secondary process dependent on advanced glomerular and tubular injury for its maximal expression (P. Lane, M.W. Steffes, S.M. Mauer, work in progress).

CONCLUSIONS

Our understanding of mesangial pathophysiology has advanced substantially through the study of renal structure and function in diabetes and type I MPGN in humans. The important processes driving the kidney towards its functional demise in diabetes are matrix accumulation in the mesangium and GBM, hyaline changes in the glomerular arterioles, and global glomerular sclerosis in diabetes and in MPGN mesangial cell expansion. Interstitial changes may also contribute to this progression. Functional alterations reflective of underlying renal pathology manifest only relatively late in the evolution of both diseases, when structural injury is already quite far advanced. Carefully designed, quantitative, prospective studies of renal pathology beginning in these and other diseases will further elucidate the specific pathologic processes important in the expression and progression of abnormalities of the glomerular mesangium in humans.

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