Perspectives in Diabetes

Mesangial Expansion as a Central Mechanism for Loss of Kidney Function in Diabetic Patients

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Diabetic nephropathy leading to kidney failure is a major complication of both type I (insulin-dependent) and type II (non-insulin-dependent) diabetes mellitus, and glomerular structural lesions (especially expansion of the mesangium) may constitute the principal cause of decline in kidney function experienced by a significant fraction of diabetic patients. Although the biochemical bases of these mesangial abnormalities remain unknown, an understanding of the natural history of diabetic nephropathy from a combined structural and functional approach can lead to greater pathophysiological insight. Work in animals has supported the concept that the metabolic disturbances of diabetes mellitus cause diabetic nephropathy, with structural and functional lesions prevented or reversed with improved or normalized glycemic control. Additional research must address this fundamental issue in humans, especially the response of advancing mesangial lesions to improved glycemic control. Factors not directly related to the metabolic perturbations of diabetes may serve to accelerate or diminish the pathophysiological processes of diabetic nephropathy. The elucidation and management of these factors, when coupled with improved glycemic control, may moderate the development or progression of diabetic kidney lesions in humans. Diabetes 38:1077-81, 1989

Our central postulate is that structural lesions of the glomerulus are the primary cause of the loss of glomerular function and kidney failure in patients with diabetes mellitus. The dominant structural change in patients with advanced diabetic nephropathy is the expansion of the mesangium, including both its cellular and matrix (or basement membrane-like) components (1–3). Enlargement of the mesangium, if not accommodated by an overall growth of the glomerulus, occurs at the expense of the glomerular capillary lumenal space and filtration surface (4,5). This scenario unfortunately happens in a significant fraction (30–40%) of patients with type I (insulin-dependent) diabetes mellitus, who then progress to kidney failure, and often, death (6). Overt diabetic nephropathy with reduced and falling glomerular filtration rate (GFR), proteinuria, and hypertension occurs only in patients with marked mesangial expansion (2) coupled with a significant reduction in glomerular filtration surface (4,5).

The scope of the morphological lesions and accompanying functional abnormalities that we have studied at Århus University and the University of Minnesota spans the natural history of diabetic kidney disease from inception of type I diabetes mellitus (1) through the demise of kidney function (2) to the recurrence of disease in transplanted kidneys (7). Surprisingly, few morphological data are available regarding diabetic nephropathy in patients with type II (non-insulin-dependent) diabetes mellitus (8), but the natural history of diabetic nephropathy may be quite similar in these patients (6,9). A substantial fraction (30–40%) of type I diabetic patients experience diabetic nephropathy leading to kidney failure, but 60–70% do not. This difference may in part be based on differences in glycemic control (10). Long-term, retrospective studies of type I and type II patients indicate that glycemic control is an important although imprecise predictor of diabetic nephropathy risk (9,11,12). Consequently, there is great need to identify other factors in addition to glycemic control that could affect the progression of diabetic nephropathy.

KIDNEY AT EARLY STAGES OF DIABETES MELLITUS

The first major structural change after onset of type I diabetes is enlargement of the whole kidney (13) and individual glo-
meruli (14). These hypertrophied glomeruli have normal structural composition. The initial characteristic pathological lesions of diabetic glomerulopathy appear only after a few years of diabetes in native kidneys (1,3) and kidneys transplanted to diabetic hosts who had lost kidney function due to end-stage diabetic nephropathy (7). The first detectable structural finding of diabetic glomerulopathy is a widening of the peripheral glomerular basement membrane (GBM), followed by an increase in the fractional volume of the mesangium, i.e., the mesangial volume as a fraction of the total glomerular tuft volume. Functionally, the GFR may be elevated over the first one or two decades, and slightly increased amounts of albumin may be excreted intermittently in the urine (15). Although these early kidney functional manifestations of diabetes mellitus may respond to improvement of glycemic control, the structural lesions in many patients progress over two or more decades of diabetes (16).

**INCREASED URINARY ALBUMIN EXCRETION (UAE) AS PREDICTOR FOR DEVELOPMENT OF ADVANCED DIABETIC NEPHROPATHY**

Several groups have reported the predictive value of slightly elevated albuminuria (called microalbuminuria) occurring in the first or second decade of type I diabetes as a harbinger of later development of clinical diabetic nephropathy (i.e., albuminuria >300 mg/24 h or ~200 µg/min, hypertension, and falling GFR) (17–20). For the most part, these investigators have used different albuminuria thresholds (from 15 µg/min in ref. 19 to 70 µg/min in ref. 20) to classify the patients retrospectively. The lower value of 15 µg/min lies at the upper limit of normal in most populations, whereas the higher value should increase the specificity by decreasing the number of false-positive samples.

A closer review of these studies (17–20) uncovered microalbuminuria and either rising blood pressure or falling GFR as important concomitants underlying the predictive value of microalbuminuria (21). For example, Mathiesen et al. (20) clearly delineated a susceptible population with progressing albuminuria and rising blood pressure. Thus, it might be argued that microalbuminuria best becomes a predictor of advanced diabetic nephropathy when it coexists with rising blood pressure and/or falling GFR. Microalbuminuria may not be a predictor of nephropathy but in fact may be an early indicator that diabetic nephropathy is already present.

**STUDIES OF KIDNEY STRUCTURE AND FUNCTION IN NORMOALBUMINURIC AND MICROALBUMINURIC PATIENTS**

We recently explored the relationship of UAE ranging from normal to 200 mg/24 h and morphometric analysis of kidney biopsies to explore the interrelationships of structural and functional kidney changes relatively early in the course of diabetic nephropathy (22). These patients spanned the functional measures seen in the earlier studies of the predictive value of microalbuminuria (17–20): GFR from elevated to normal to subnormal levels, UAE from normal to elevated (and even hypertensive) blood pressure measurements. Patients with normal albuminuria or microalbuminuria and normal values for creatinine clearance and blood pressure had GBM widths and volume fractions of the mesangium ranging from normal to significantly increased. Thus, normal measures of kidney function in diabetic patients may not indicate normal structure in the kidney. Furthermore, from our previous work in Århus (5) and Minneapolis (2), we would expect clear functional evidence of diabetic nephropathy to appear in some of the patients if the already substantial mesangial expansion progresses. In contrast, microalbuminuria may be present in patients with no measurable kidney structural abnormalities despite >20 yr of diabetes. We would expect such patients to have a good prognosis.

Patients with microalbuminuria and decreased creatinine clearance and/or hypertension uniformly demonstrated widening of the GBM and expansion of the mesangium. In the earlier studies (19,20), many patients with microalbuminuria who proceeded to clinical diabetic nephropathy would have been included in this group on the basis of functional criteria. Thus, microalbuminuria accompanied by hypertension and/or decreased GFR indicates established glomerular structural changes and in this way marks patients who have early clinical nephropathy. Note that such patients in our study regularly had UAE rates >45 mg/24 h (~30 µg/min), and this observation likely explains some of the previously published results (17,18,20). However, it is not clear why one group found a substantially lower UAE rate of 15 µg/min to be a risk discriminator (19).

**GLOMERULAR STRUCTURE AND DEMISE OF KIDNEY FUNCTION**

We have shown that the area of the peripheral capillary surface is precisely and directly related to the GFR over the spectrum from early to advanced diabetic nephropathy (4,5,14). A typical biopsy in a patient with advanced diabetic nephropathy and declining kidney function will contain hyalinized, obliterated glomeruli and open glomeruli with marked mesangial expansion (Fig. 1). The peripheral capillary surface available for filtration in the open glomeruli and the percentage of nonfunctional, hyalinized glomeruli can be measured. Because the absolute number of glomeruli in a patient cannot be determined, inferences must be made based on the percentage of hyalinized glomeruli. Nevertheless, an ensuing estimation of total peripheral capillary surface per patient (assuming an initially identical number of glomeruli per patient) related well to GFR (4,5,23).

Also, consider the implications of mesangial expansion leading to overt nephropathy against the striking background of the article by Borch-Johnsen et al. (24), who found increased mortality in patients experiencing overt proteinuria. Thus, virtually all of the increased mortality in type I diabetes occurs in patients who develop proteinuria and presumably mesangial expansion, whereas type I diabetic patients without proteinuria have age- and sex-connected mortality rates nearly equivalent to the background nondiabetic population. The increased mortality of the nephropathic type I diabetic patient largely arises from the consequences of uremia and from accelerated macrovascular disease.

Our work with the structural and functional natural history of diabetic nephropathy has identified the expansion of the mesangium and the reduction in peripheral capillary surface as constituting the mechanism leading to the demise in kidney function (2,4,22). GBM width did not correlate with peripheral capillary surface (2). As was true in rats (25), the
width of the GBM in diabetic patients does not correlate well with the magnitude of UAE or other measures of kidney function. Normal UAE can occur with a widened GBM in both diabetic patients receiving standard insulin therapy (2) and rodents after successful islet transplantation (25). Diabetic patients experiencing significant proteinuria may not uniformly evince the widest GBMs. Therefore, hypotheses concerning the nature of the matrix constituents of the GBM as the central modulator of the filtration barrier must accommodate the fact that a very thick GBM can be part of a functionally effective barrier. On the other hand, marked mesangial expansion is uniformly associated with proteinuria (2). Yet, like the GBM, the mesangium can undergo expansion beyond the normal range and still not affect kidney function (22); in other words, the functional resiliency of the nephron in the diabetic subject can maintain normal values in standard kidney function tests even with clear structural lesions. One intriguing area to be explored lies at the possible interaction of a markedly expanded mesangium on the barrier integrity of the GBM (26). Little or no information concerns the manner in which the expanded mesangium may change the level of UAE; e.g., why do some patients with demonstrable mesangial expansion still enjoy normal UAE versus others with dipstick-positive proteinuria and similar mesangial lesions?

The role of the mesangium in affecting peripheral capillary surface is best understood when factored by the glomerular volume as Bilous et al. have shown (p. 1142, this issue). It appears that the mesangium expanding into an inherently large or perhaps secondarily enlarged glomerulus will less affect peripheral capillary surface than the same mesangium volume in a smaller glomerulus (4, 5, 27). This postulate presumes a limited volume within the glomerulus for the structures contained therein. Thus, the change in one component of the glomerulus must affect the volume available to other structures, e.g., glomerular capillaries. Mechanistically the mesangium impinges on the peripheral capillary surface, and with sufficient pathological expansion, the enlarging mesangium will eventually compromise filtration surface and reduce GFR. These structural factors may reflect separate pathophysiological or protective mechanisms affecting the development of diabetic glomerular disease. As an example, the mesangium in a diabetic patient may expand at a rate influenced by the degree of hyperglycemia and the intrinsic response of the mesangium to hyperglycemia. In some patients, at a given level of hyperglycemia, the mesangium may expand very slowly or not at all. In other diabetic patients with similar glycemic control, the mesangium will expand so rapidly as to compromise kidney function. Thus, it appears that the point at which the rapidly enlarging mesangium reduces peripheral capillary surface and thereby compromises kidney function may be determined by the original size of the glomerulus or the capacity of the glomerulus to enlarge when filtration surface is threatened by an enlarging mesangium.

GLYCEMIC CONTROL AND STRUCTURAL LESIONS OF DIABETIC NEPHROPATHY

Whether glycemic control determines the rates of progression or amelioration of the structural or functional abnormalities of diabetic nephropathy in humans remains a major research question. In rats, mesangial lesions and albumi-
nuria can be prevented with optimal glycemic control by insulin injections (28,29; see ref. 25 for review). They can also be reduced to normal levels after successful islet transplantation (30,31). In contrast, GBM widening can be prevented (32) but not reversed (33) with normalization of plasma glucose levels.

Little information has been gathered on the efficacy of improved glycemic control on the progression of the structural lesions of diabetic nephropathy in humans. Retrospective analysis of biopsies from long-term kidney transplants in diabetic patients revealed a threshold of ~13 mM (230 mg/dl) glucose in plasma, above which half but not all kidneys had mesangial expansion by light microscopy (10). Below these very high levels of plasma glucose, measures of glyceria were not correlated to the rate at which the lesions developed. These observations took place against a spectrum of lesions in kidneys transplanted to diabetic hosts that reflected the full range of structural lesions in native kidneys of diabetic patients (2,5,7). Prospective studies to evaluate the efficacy of improved glycemic control on diabetic lesions in native or transplanted kidneys must follow these initial observations.

In addition to the basic issue of glycemic control and the progression or reversal of diabetic glomerular lesions, the magnitude and characteristics of structural change that still can be reversed must be addressed. What stage(s) of mesangial expansion can be diminished or ameliorated with establishment of normoglycemia? The observations of Feldt-Rasmussen et al. (34) may permit an inferential and speculative answer. They demonstrated a halt in the progression of albuminuria with improved but not perfect glycemic control. The level of albumin excretion in their patients, compared to the observations of Chavers et al. (22), suggests the presence of well-established mesangial lesions in the Danish patients. Consequently, the stabilization of albuminuria demonstrated by Feldt-Rasmussen et al. may be compatible with arrest of mesangial lesions, whereas patients with higher levels of glycosylated hemoglobin progressed to overt nephropathy.

**FUTURE DIRECTIONS**

To better understand the pathophysiological foundation of diabetic nephropathy, we must prospectively observe patients with differing rates of development of disease. Data from animal models of diabetic nephropathy or strictly biochemical studies must be related to the natural history of important structural and functional alterations of the kidney in diabetic patients. Elucidation of the natural history of diabetic nephropathy, manifested by an evolution of biochemical, structural, and functional lesions, remains a primary goal in understanding pathophysiological principles and constructing recommendations for the management of the patient. Given the average two-decade duration over which glomerular lesions destroy kidney function in humans, the goal outlined above is difficult to achieve but necessary to pursue. Although it may be difficult to prove or disprove a hypothesis in patient populations, the application of postulated pathophysiological mechanisms based on biochemical or animal experiments will ultimately depend on research in patients with diabetes. Much of this research will require integrated studies of function and structure revealed by kidney biopsy.

**REFERENCES**

34 Feldt-Rasmussen B, Mathiesen ER, Deckert T. Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. Lancet 2:1300–304, 1986