Diabetic Nephropathy: a Disease Causing and Complicated by Hypertension

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In examining the pathophysiology underlying the development of hypertension in diabetes mellitus, it is important to draw clear distinctions between Type I and Type II diabetes. In patients with Type I diabetes, with a peak onset of disease early in the second decade of life, hypertension clearly represents the sequelae to the development of substantial renal lesions, especially in the glomerulus. Thus the prevalence of hypertension in those patients without substantial glomerular lesions approximates the incidence of hypertension in the general population (~4%). In patients with Type II diabetes mellitus and onset generally later in adult life, an increase in blood pressure can often be demonstrated early after or even before diagnosis of the disease (most readily demonstrated in the Pima Indians). Furthermore, clear familial tendencies towards the development of nephopathic complications of diabetes can be shown. In patients with Type I disease, the fall in glomerular filtration rate parallels the fall in glomerular capillary surface available for filtration. This reduction in the peripheral glomerular capillary surface correlates well with the expansion of the mesangium, strongly implicating the mesangial expansion in the demise in renal function. For both Type I and Type II diabetes mellitus, the increase in albuminuria may reflect an opening of large pores in the glomerular basement membrane, thereby allowing serum proteins to cross into the filtration space.

Diabetic nephropathy (both the function and structural manifestations of a complex of renal lesions) occurs only in patients with diabetes mellitus (either Type I or Type II disease, i.e., insulin-dependent or not). Thus the lesions basically must relate to the metabolic abnormalities involved in diabetes (or to their consequent biochemical alterations at the organs susceptible to the complications). Most of this paper refers directly to observations in Type I diabetes mellitus; however, we will also discuss Type II diabetes mellitus, especially with regard to hypertension and its manifestation and influence on the development of diabetic nephropathy.

The initial functional alterations of diabetic nephropathy—increased glomerular filtration rate (GFR) and increased urinary excretion of albumin—can for the most part be reversed by improved glycemic control (1). Nevertheless, in some patients an above-normal GFR may persist, in part because of the increased intake of protein seen in diabetic patients (2). Within the first three to five years of Type I diabetes, morphological lesions of the glomerulus can be demonstrated (3). The first measurable lesion is the widening of the glomerular basement membrane (GBM). The expansion of the mesangium follows and encompasses the fundamental lesion, leading to a decline in renal function in a substantial fraction of patients (4).

Although the structural and functional lesions of diabetic nephropathy require the occurrence of diabetes mellitus, other factors, many of which remain unknown at present, must modulate the effect of diabetes on the initiation and progression of the renal lesions (5, 6). These factors are quite probably familial (7) and reflect the influence of genetically determined processes. Because normal glyceria is difficult to attain in nearly all patients with either Type I or Type II diabetes mellitus, new approaches must be sought to manage the complications of diabetes separate from treating the basic disease. The definition of these determinants affecting the progression of diabetic complications (and consequent development of new therapeutic strategies) will add important information to the management of diabetic nephropathy.

In understanding the pathophysiology of diabetic nephropathy in humans, one must account for the extended natural history of this disease. In the large fraction of patients with Type I disease who ultimately face the loss of renal function, the peak incidence of renal disease (when substantial proteinuria can be demonstrated) occurs after 15 to 20 years of diabetes (8). Before reaching this stage, a patient experiences an initial extended period of above-normal GFR, eventually accompanied by a small increase in urinary albumin excretion (so-called "microalbuminuria") with a rising blood pressure. These conditions are followed by a decreasing GFR and marked albuminuria readily detectable by routine screening techniques (8). With the development of clinically apparent diabetic nephropathy (marked albuminuria/proteinuria, a falling GFR, and frank hypertension), patients often follow a downward course, leading to eventual renal failure. At this stage of disease, the patient faces a relative mortality approaching 100-fold that from renal and cardiovascular disease (8). The only potentially beneficial therapy to slow the progression of renal disease is the application of antihypertensive medications to normalize blood pressure (9). The risk of death from nonrenal complications probably remains high, even with appropriate therapy for hypertension. Although far less information is available on nephropathy in Type II diabetes mellitus, its course may be similar to that in Type I diabetes, or even faster (10). A substantial fraction of the large number of diabetic patients undergoing hemodialysis have Type II disease.

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In the following sections we will first present a patient whose situation underlines the dilemma between structural and functional measures that may occur during the course of diabetic nephropathy. We will then discuss the pathophysiologic basis of the decrease in GFR and the increasing excretion of albumin in urine. We will conclude with a discussion of the important role hypertension may play in the progression of diabetic nephropathy in both Type I and Type II diabetes mellitus.

Patient with Type I Diabetes Mellitus and Diabetic Nephropathy

The following case summary illustrates the structural and functional pathology of diabetic nephropathy and the potential benefit of antihypertensive agents in lowering blood pressure and reducing albuminuria to near-normal values. A 27-year-old man with a 15-year history of Type I diabetes mellitus underwent evaluation for pancreas transplantation. He was experiencing proliferative retinopathy and peripheral neuropathy, and during the previous year he had begun receiving a diuretic for borderline hypertension. The following laboratory values were obtained: blood pressure, 119/81 mmHg (average of n = 9 readings while he was taking the diuretic); hemoglobin A1c, 7.1% (normal, 4.3–6.1%); urinary albumin excretion, 20, 30, and 49 mg/24 h (normal, <30 mg/24 h); creatinine clearance, 50, 86, and 98 mL/min per 1.73 m² of body surface area (normal, 110–150 mL/min per 1.73 m²). A renal biopsy from this patient demonstrated the classical findings of diabetic nephropathy, including a widened GBM width (671 nm; normal, 250–450 nm) and substantial expansion of the mesangium, occupying nearly 40% (normal, 4–22%) of the glomerular volume (Figure 1). The mesangial expansion reduced the peripheral capillary surface, causing the indicated reduction in GFR.

All the findings summarized for this patient, except his urinary albumin excretion, describe a picture of advanced (and probably progressing) diabetic nephropathy. The effective use of antihypertensive medication quite likely reduced (and nearly normalized) the albumin excretion. Much current speculation has addressed the efficacy of improved glycemic control vs antihypertensive therapy in ameliorating above-normal urinary albumin excretion and the course of diabetic renal disease (9). However, the assumption that a nearly normal albumin excretion indicates a resolution of the fundamental renal pathological changes was not supported by the findings from the renal biopsy in this patient. Rather, the mesangial expansion demonstrated in this patient approached a level regularly associated with advanced morphological changes accompanied by hypertension, a decreasing GFR, and marked albuminuria (4). Thus the near-normal urinary albumin excretion found after initiating antihypertensive medication does not allow one to conclude that the underlying renal pathology is only moderate.

Etiology of the Decrease in GFR in Diabetes Mellitus

The natural history of GFR in Type I diabetes mellitus follows an interesting course of an initial increase early in disease, especially before any therapy with insulin (1). To some extent, this early rise can be ameliorated with appropriate insulin therapy to reduce the hyperglycemia. Nevertheless, many patients have a consistently high GFR, potentially related to glycemic control but also associated with and responsive to protein (or possibly amino acids, after proteolysis) in the diet (2, 11). The hyperfiltration may continue for as long as a decade or more of Type I diabetes. Some reports suggest that patients with hyperfiltration are those most likely to proceed to developing end-stage diabetic nephropathy (12), but this observation has not been confirmed by others (13). During the course of diabetic nephropathy, as was seen in the patient above, the GBM widens and the mesangium expands—in many patients, significantly. The expansion of the mesangium results in a reduction in the peripheral capillary filtration surface (4, 14), which correlates directly with a decrease in GFR (15, 16). Any factors that reduce the effect of the mesangium on the filtration surface, e.g., the capacity to enlarge the glomerulus, or an initially large glomerulus (6), may modulate the impact of mesangial expansion on GFR. Nevertheless, in a substantial fraction of patients, the inexorable expanding mesangium appears to result in an increasingly severe compromise of the surface available for filtration, eventually resulting in renal failure for the patient.

The only known treatment to ameliorate the decreasing GFR is appropriate and aggressive antihypertensive therapy (9). The efficacy of antihypertensive medications at this stage of disease potentially is related to the lowering of the systemic blood pressure (and potentially the intraglomerular capillary pressure) that may progressively accelerate the destruction of the kidney and
renal function. Although many experiments in animals and humans have compared the efficacy of classes of antihypertensive medications in diabetic renal disease, there has been no demonstrable benefit of one drug over another (17, 18). Rather, the success of an agent or combination of agents rests on their ability to lower blood pressure. At this point in the development of diabetic renal disease, the end result may be a common pathway that ultimately leads to destruction of glomerular function (17). Potentially it is this common pathway that can be ameliorated with antihypertensive agents.

Etiology of Albuminuria/Proteinuria in Diabetes Mellitus

The presence of albumin in the urine, especially at low concentrations (microalbuminuria) early in the course of Type I diabetes mellitus, could result from either glomerular or tubular dysfunction. Only by exquisite micropuncture techniques in rodents can these possibilities be separated. Therefore, extrapolating evidence in animals to the understanding of normal renal function and of the aberrations occurring with disease in humans remains speculative at this time. Modest amounts of protein leaked from glomeruli into the urinary space can be substantially resorbed by the renal tubules. Thus the nature of microalbuminuria and, specifically, of changes in the charge arrays of protein in urine in diabetes mellitus may either reflect a change in the barrier wall of the glomerulus to charged proteins or result from a selective reabsorptive process in the tubule for proteins of a particular charge. The conclusion that an increase in negatively charged immunoglobulins could come from a lack of negative charges in the glomerular filtration barrier (19) could also be explained by a failure of the tubule to resorb these negatively charged proteins (20).

We find that the best explanation for the process of albuminuria/proteinuria in diabetes is in the model established by Myers et al. (20, 21). Their basic model relies on the creation of a bimodal distribution of pores in the glomerular filtration barrier, changing with progression of diabetic renal disease; to date, they have not focused on changes in tubular function. The change in pores at the glomerular barrier involves the introduction of large, essentially indiscriminate, pores in the glomerular barrier, thereby permitting the development of albuminuria/proteinuria. The regular array of small pores present in the glomerulus (modeled to be ~5.5 nm in diameter) remains unchanged. Pores of this diameter with the appropriate charge properties are highly effective in excluding albumin from the urinary space. However, when increasing fractions of the glomerular barrier are occupied by large, indiscriminate pores, there can be substantial leakage of protein of all sizes and charges, resulting in the albuminuria and immunoglobulinuria measured in Type I diabetes mellitus (20). Using this model, Myers et al. (20, 21) found a good correlation between the leakage of albumin and immunoglobulins in the urine and the fraction of the barrier occupied by these large and indiscriminate pores (determined by modeling techniques based on the data obtained from infusion of uncharged dextran molecules into the blood and collection of these molecules in the urine). Although no anatomical evidence for the presence of such pores exists, they remain an important theoretical (and currently pragmatic) construct for understanding the role of proteinuria in the natural history of diabetic nephropathy. This construct is now being applied to explain the early excretion of albumin found in Pima Indians with Type II diabetes mellitus (22, 23) and has been used quite effectively in understanding the process of urinary protein excretion in other renal diseases.

Hypertension in Diabetes Mellitus

The earlier sections suggested similarities of the appearance of albuminuria and the decrease in GFR in Type I and Type II diabetes mellitus. Although the advancement of the glomerular lesions in both Type I and Type II diabetes mellitus can lead to hypertension, any discussion of hypertension in diabetes must draw clear distinctions between patients with Type I or Type II disease. For the most part, patients with Type I diabetes mellitus contract the disease in childhood (peak onset at age ~12 years). Patients with Type II disease frequently will not manifest diabetes until their fifth or sixth decade or even later. Thus, the greater prevalence of hypertension and cardiovascular disease in general in older diabetic patients will obfuscate the causes underlying a rising blood pressure and will confound the effects of diabetic renal disease on hypertension. Thus, many patients with Type II diabetes may already be experiencing pre-existing hypertension, which may synergistically accelerate the development of nephropathy in these patients. Some evidence indicates that, in the Pima Indian population, hypertensive disease or a tendency to a higher blood pressure at the onset of diabetes may increase the risk of diabetic nephropathy. Finally, a familial relationship exists between manifestations of diabetic renal disease in diabetic parents and the development of nephropathy in their diabetic offspring (22).

The basic etiology of hypertension in diabetes mellitus remains unknown. Renal production of vasoactive agents and the kidney's role in managing electrolyte balance are both important determinants of blood pressure (24). However, attempts to define changes in renal-derived peptides that ultimately lead to increased blood pressure in diabetic patients have been, for the most part, inconclusive (24). Except for those patients with pre-existing essential hypertension, a high blood pressure that complicates diabetes mellitus arises from the diabetic state. The incidence of essential hypertension in Type I diabetes is the same as that of the nondiabetic population (25). In the Pima Indian population with Type II diabetes, 92% of patients with hypertension have a diabetes-related etiology (26). Thus, in the great majority of diabetic patients, hypertensive disease must arise from microvascular, macrovascular, or renal disease itself. As the renal disease progresses in patients
with Type I diabetes mellitus, albuminuria increases, GFR eventually begins to decrease, and mounting evidence indicates that early in the course of the disease an increase in blood pressure can be demonstrated (27, 28). With the advancing of the renal lesions of diabetes mellitus, essentially 100% of patients with Type I diabetes who experience albuminuria (albumin >300 mg/day) and a decreasing GFR will have coexisting hypertensive disease (4). As alluded to above, these functional abnormalities will coexist with advanced structural lesions (4, 29).

In Type I diabetes mellitus, recent efforts have been made to link the sodium–lithium or sodium–hydrogen countertransport mechanisms with the presence of hypertensive disease in diabetes mellitus (5, 30). Because changes in cation transport have been demonstrated to influence the prevalence of other kinds of hypertensive diseases (31), it has been appealing to apply this finding to the etiology of hypertensive disease in diabetes mellitus. Two groups have suggested that hypertensive disease in parents and the increase in sodium–lithium countertransport activities are predisposing factors to the development of diabetic nephropathy in Type I diabetes mellitus (5, 30, 32). Each study demonstrated statistical differences between the groups, but the biological implications of these observations remain uncertain because the absolute differences were quite minor. In addition, a recent report from Steno Memorial Hospital in Denmark (33) has clearly demonstrated an increase in sodium–lithium countertransport activity in Type I diabetes mellitus, there being little difference between those patients with diabetic nephropathy and those without. The authors of that paper emphasized the potential relationship between glycemic control and sodium–lithium countertransport. This matches many other observations suggesting that those patients with or predisposed to diabetic nephropathy have poorer glycemic control than those patients not experiencing this complication (34–36). In addition, the Steno paper (33) failed to demonstrate any familial predisposition to hypertension or increased sodium–lithium countertransport activity in parents of patients who experienced diabetic nephropathy.

The relationship of an initial increase in blood pressure to increased urinary albumin excretion remains somewhat elusive. Mathiesen et al. (27) demonstrated an increase in urinary albumin excretion before a measurable increase in blood pressure. Weigmann et al. (28), measuring ambulatory blood pressure, found an increase in blood pressure in Type I diabetic patients at all times of day, but particularly overnight. Further, by standard procedures, they found no differences in blood pressure between normal and diabetic subjects, whereas they could readily demonstrate differences by using ambulatory blood pressure measurement techniques. They suggested that increases in ambulatory blood pressure may be prevalent in Type I diabetes mellitus. Thus the exposure of diabetic patients to above-normal intravascular pressure may occur 24 h a day, although the increase in pressure burden may be especially accentuated in sleep (28). However, one must emphasize that the patients Weigmann et al. studied were quite poorly controlled, with hemoglobin A1c measurements averaging 11%. Thus their patients may have evinced a hypertensive response to poor glycemic control. Additional studies to compare the effects of improved glycemic control within and between populations can address this important issue. Another important corollary of their study is the need to use these modern techniques of blood pressure measurement to evaluate prospectively a population of diabetic patients as they move from totally normal renal function through increased urinary albumin excretion, with or without concomitant increase in ambulatory blood pressure measurements, to frank changes in renal function.

In Type II diabetes mellitus, the progression of diabetic renal disease leads to an increased prevalence of hypertension. However, pre-existing hypertensive disease is frequently seen in this population, because of their older age. In the Pima Indian population, as discussed above, pre-existing hypertension, familial tendency towards increased blood pressure, or both (37), lead to an increased incidence of diabetic nephropathy. The separation of these factors in that population has not been definitively achieved. Thus, more epidemiologic studies must be completed before these factors can be successfully dissected. Nevertheless, in both Type I and Type II diabetes mellitus, the progression of glomerular disease is nearly always associated with an increasing blood pressure and finally with the evolution of renal disease, including hypertension.

Much remains to be determined about the interrelationships of the functional expressions of diabetes mellitus and the structural measures underlying them. There is a strong need for prospective studies that monitor a carefully chosen group of patients to demonstrate the interrelationships among the structural and functional variables, and among the functional variables themselves (29). In addition, the relationship between glycemic control and the development of these structural and functional manifestations of disease must be elicited. Major questions to be answered are (a) at what level of glycemic control and (b) when in the pathophysiological course of Type I or Type II diabetes mellitus, can the development of these life-threatening diabetic complications be ameliorated in a substantial fraction of the patient population?

References
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