Diabetic Nephropathy
A Perspective

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SUMMARY

The earliest manifestations of clinical diabetic nephropathy, including proteinuria, hypertension, and declining GFR, represent very advanced diabetic glomerulopathy with especially prominent mesangial expansion. Mesangial expansion, by restricting glomerular capillary filtration surface and lumenal volume, stimulates compensatory mechanisms analogous to those resulting from a marked reduction in nephron number. These compensatory mechanisms involve alterations in glomerular hemodynamics designed to maintain glomerular filtration but which ultimately injure the kidney. These hemodynamic perturbations are not specific to diabetes but represent a final common pathway toward endstage renal failure that also characterizes the remnant kidney. This thesis concludes that the onset of clinical diabetic nephropathy augurs inevitable decline in kidney function, and that only studies and interventions exercised before clinical nephropathy develops can influence understanding and outcome of diabetic nephropathy. DIABETES 32 (Suppl. 2):52–55, 1983.

This paper attempts to integrate current information derived from human and animal studies of diabetic nephropathy into a series of testable hypotheses concerning the pathogenesis of diabetic nephropathy and an approach to patient evaluation. To this end, we will review aspects of our own work and borrow heavily from the work of others, many of whom have contributed to this symposium. Undoubtedly, this speculative approach will raise serious controversies since several conceptual leaps are taken. However, it is hoped that this effort will crystallize important questions which, when answered, will expand our understanding of diabetic nephropathy and other renal diseases.

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DIABETIC NEPHROPATHY: A DEFINITION

Diabetic nephropathy is defined as a multifaceted pathologic entity which spans the continuum from early renal hypertrophic changes to late stages of advanced structural distortion of glomeruli, renal vasculature, interstitium, and tubules.[1] We argue that the classical clinical manifestations of this pathologic entity, overt continuous proteinuria, hypertension, and declining GFR,[2,3] represent nonspecific consequences of this continuum. Useful markers of the extent of renal structural changes, they are not specific for diabetes.

SPECIFICITY OF THE PATHOLOGY OF DIABETIC NEPHROPATHY

The advanced lesions of diabetic nephropathy are, in their constellation, specific. Taken separately, many of the component abnormalities, such as glomerular basement membrane (GBM), tubular basement membrane (TBM),and mesangial thickening can be seen in a variety of renal disorders, although the characteristics of diabetic GBM thickening as seen by electron microscopy are rarely seen in disorders other than diabetes.[4] Finding these changes along with afferent and efferent arteriolar hyalinosis, increased renal linear extracellular membrane albumin, and IgG localization are diagnostic of diabetic nephropathy.[1] The nodular lesion of Kimmelsteil and Wilson, itself considered a diagnostic finding, represents advanced mesangial thickening and, as such, does not reflect unique pathogenetic mechanisms. The specificity of diabetic nephropathy is highly significant. Based upon animal studies, it is suggested that the lesions of diabetic nephropathy develop as a consequence of altered renal hemodynamics.[5] This argument is provoking since, for many years, the insulin-dependent diabetic patient maintains increased glomerular filtration rate (GFR),[6] microalbuminuria with exercise,[6] or at rest,[7] and enlarged renal size.[6] It would be expected that, if hemodynamic consequences alone can provoke the lesions of diabetic nephropathy, these lesions would be visible in a variety of circumstances in which the nephron population has been markedly reduced

for many years, leading to compensatory hyperperfusion of residual glomeruli.[8] However, our extensive experience in the study of endstage kidney disease in man does not suggest this course of events. The pathology of the "remnant kidney" model of nephron destruction in rats has only superficial resemblance to diabetic nephropathy in this species.[5,9] Uninephrectomy in normal rats produces glomerular hemodynamic alterations in the same direction and to at least the same degree as diabetes in the intact rat, yet the uninephrectomized rat does not develop lesions of diabetic nephropathy despite prolonged observation.[10] The diabetic rats with the most marked hemodynamic alterations are insulin-treated,[5] and this treatment markedly reduces diabetic nephropathy.[11] The untreated diabetic rat has diminished single-nephron pressures and blood flows[5] yet demonstrates more severe nephropathy than the insulin-treated animal.[11] Based upon our studies of uninephrectomized[10] or hypertensive[12] rats and uninephrectomized dogs[13] with diabetes, we are convinced that hemodynamic factors can influence the *rate* at which the specific lesions of diabetic nephropathy develop. However, the *direction* of the nephropathology of diabetes is unique to diabetes.

THE NATURAL HISTORY OF DIABETIC NEPHROPATHY

The subtle abnormalities of renal function highlighted by increased GFR, characteristic of almost all insulin-dependent diabetics,[6] persist for many years[6] and are unremitting in those apparently escaping severe nephropathy.[6,14] The magnitude of the increase in GFR has not been shown to predict nephropathy risk, although this increase is inversely related to glycemic control.[6,14,15] This prolonged, clinically silent period challenges certain theoretical considerations of the fundamental nature of diabetic nephropathy. Given the gradual progression of GBM thickening with time, more detailed understanding of the chemistry of this thickened structure in diabetes might not explain the alterations in glomerular permselectivity which herald the final downhill course of the diabetic with severe nephropathy.[3,16] Otherwise, one would expect a gradual increase in proteinuria as GBM thickening develops. Our preliminary studies of functional-structural relationships in diabetes[16] indicate that marked GBM thickening is compatible with intact permselectivity while minimal GBM thickening can be associated with massive proteinuria. Our observations concur with those of Gellman et al.,[17] who point out that the salient clinical manifestations of diabetic nephropathy, proteinuria, hypertension and, ultimately, decreased GFR, are best related to the severity of diffuse mesangial thickening than to any other single morphologic feature of diabetic nephropathy.

THE REMNANT KIDNEY HYPOTHESIS AND DIABETIC NEPHROPATHY

The remnant kidney hypothesis, based on physiologic studies in animals[18] and clinical observations in man,[19,20] suggests that compensatory mechanisms to reduced numbers of nephrons result in the establishment of hemodynamic forces within the glomerulus that disrupt structure to produce functional consequences including proteinuria and hypertension. These forces ultimately lead to further nephron destruction.[18] The influence of hypertension on the rate of decline of GFR in the nephropathic diabetic patient[21] is consonant with this hypothesis but not specific to diabetes. The clinical manifestations of diabetic nephropathy, overt proteinuria, hypertension, and declining GFR have, at their onset, essentially no relationship to the number of hyalinized glomeruli.[16] Yet the remnant kidney hypothesis may be key to the development of clinical diabetic nephropathy. If one extends the hypothesis to include mechanisms operative when the capillary luminal space and the peripheral capillary filtering surface of glomeruli are diminished as a consequence of marked mesangial expansion, one can envision the remnant kidney pathophysiology operative in situations in which the number of "functioning" glomeruli is not significantly reduced. In other words, if the renal responses to reduced numbers of glomeruli and to reduced filtration surface and capillary luminal space with normal numbers of glomeruli are the same, both situations could result in similar destructive forces. The similarities in alterations of the permselectivity characteristics of the glomerular filter in the remnant kidney model in rats[22] and in clinical diabetic nephropathy in man[23,24] are remarkable. Key to the support of this hypothesis is the finding that clinical diabetic nephropathy manifests itself only when the structural lesions of diabetic nephropathy are very advanced. One can predict with certainty that overt proteinuria in diabetic nephropathy is associated with marked structural changes including a diminution of 50% or more in peripheral capillary filtration surface and fractional capillary luminal volume in nonhyalinized glomeruli.[16] Consonant with this hypothesis is the finding that clinical diabetic nephropathy may become manifest when advanced diabetic glomerulosclerosis is present in the absence of occluded (hyalinized) glomeruli.[16] These considerations are at variance with those of Gunderson and Østerby, who argue that clinical manifestations of diabetic nephropathy are closely related to the numbers of occluded glomeruli and that residual glomeruli have little mesangial expansion and wide open glomerular capillaries.[25] These discrepant views are perhaps best explained by the more advanced deterioration in glomerular function in the patients of Gunderson and Østerby.[25] It is not surprising that as the kidney approaches endstage in diabetes the nonhyalinized glomeruli would reflect that population of glomeruli relatively spared of mesangial widening. Central to our argument is that overt proteinuria, hypertension, and declining GFR can all manifest in patients with advanced mesangial lesions who have less than 10% hyalinized glomeruli.[16]

THE IRREVERSIBILITY OF CLINICAL DIABETIC NEPHROPATHY

If the remnant kidney hypothesis of diabetic nephropathy is correct, it would predict that once clinical diabetic nephropathy is present it is unlikely to be reversed by steps taken to influence the diabetic state. The structural glomerular changes have established compensatory mechanisms which lead to progressive glomerular injury independent of the diabetic state. Once overt clinical nephropathy has developed, efforts to improve glycemic control have generally been unsuccessful in influencing the downhill course of the kidney disease.[26] It is consonant with this hypothesis that treatment of hypertension slows the progression of clinical diabetic nephropathy,[21] since this therapeutic maneuver slows the destruction of the remnant kidney model in rats[27] and since

treatment of hypertension could well diminish physical forces within the glomerular circulation that disrupt glomerular structure.

THE DILEMMA OF THE REMNANT KIDNEY HYPOTHESIS OF CLINICAL DIABETIC NEPHROPATHY

We maintain that clinical diabetic nephropathy is a late manifestation of diabetic nephropathy and is subsumed by the physical forces which develop as a consequence of restricted glomerular circulation and filtration surface resulting from mesangial expansion. These consequences of mesangial expansion may be aggravated by irreversible glomerular hyalinization. Thus, the functional changes are the result of incompletely understood compensatory responses to the structural lesions of advanced diabetic nephropathy. It follows that removal of the root cause of the structural changes, the diabetic state, will not alter the new set of forces now destructive of the glomerulus. It is hypothesized that, once clinically manifest, the progression of diabetic nephropathy is independent of the diabetic state. Preliminary evidence of Viberti et al.[26] supports this view. Thus, to prevent progressive renal failure manipulation of the diabetic state must be instituted before clinical diabetic nephropathy is evident.

To prevent renal failure in IDDM, the diabetic state and its consequences must be managed differently than heretofore in all IDDM patients or factors predictive of high risk for nephropathy in individual patients must be uncovered. Since approximately 60% of IDDM patients escape clinical nephropathy,[28,29] since current modes of improved diabetic control are difficult,[30] and since the precision of control required to prevent secondary complications in the individual patient is unknown,[30] it is reasonable to search for nephropathy risk factors, including the magnitude of increase in GFR, kidney size, and microalbuminuria at rest or with exercise. Since all of these subtle renal abnormalities in diabetes are markedly and swiftly influenced by glycemic control,[7,14] it seems reasonable to approach these studies in patients with uniform metabolic regulation. In this way, it may be possible to discover whether the patients with the greatest increase in GFR, kidney size, or microalbuminuria for any given level of hyperglycemia are at greatest risk of nephropathy. Clearly, other potential predictors of nephropathy risk such as alterations in blood rheology[31] and platelet function[32] merit consideration.

A dilemma arises when approaches to the measurement of risk are considered. Longitudinal prospective studies are fraught with difficulties of patient acquisition, cooperation, and compliance, and investigator exhaustion. Long-term studies become obsolete with new developments in the field. Cross-sectional studies are weakened by gaps in knowledge of the patient's relevant medical history. One possible solution is the evaluation of renal biopsy material. A logical approach can be developed if we accept the assumption that for any given duration of disease IDDM patients with the most severe lesions are at the highest risk of clinical nephropathy. This assumption is reasonable, as IDDM patients do not develop renal failure from diabetic nephropathy without the development of very advanced pathologic lesions of diabetic nephropathy. It is not unlikely that the only sufficiently accurate predictor of risk of diabetic nephropathy will, in fact, be the findings on renal biopsy. This may be considered to be a very unfortunate state of affairs. However, we do not share this view. There is no other progressive, primarily glomerular disorder with such a high risk of renal failure in which there is such reluctance to perform renal biopsies as IDDM. If the onset of clinical nephropathy represents the beginning of the end of useful function of the kidneys in diabetes, it may only make sense to perform renal biopsies before renal disease is clinically detectable.

THE GENETIC HYPOTHESIS REVISITED

Based primarily on the findings of increased muscle capillary basement membrane thickness (CBMT) in the offspring of conjugal diabetics who were not themselves diabetic, Siperstein argued that the secondary microvascular complications of diabetes are independent of the metabolic disturbances of diabetes and represent a separately inherited disorder genetically linked to the diabetic state.[33] This hypothesis has generated enormous controversy and is not generally accepted.[34–36] The major attacks on the Siperstein hypothesis have come from a variety of animal and human studies indicating important relationships between the severity of the diabetic state and the rate of development of microvascular complications.[1] Perhaps the strongest argument against this hypothesis is the development of all of the changes of diabetic nephropathy in related and nonrelated renal allografts transplanted into diabetic patients.[37,38] Our preliminary observations that regression of major lesions of recurrent diabetic nephropathy in renal allografts follows pancreas transplantation (unpublished data) further weakens the argument that diabetic microvascular complications are independent of the dysmetabolism of diabetes. Nonetheless, it must be acknowledged that patients of the same age, sex, duration of diabetes, insulin dose, and history of diabetes control can demonstrate remarkable differences in severity of diabetic nephropathology. It is certainly possible that these differences represent markedly variable individual susceptibility to tissue injury resulting from diabetes, and that this variability is genetic in origin. As mentioned, changes of diabetes occur in the normal kidneys transplanted into diabetic patients.[37,38] While patients transplanted because of diabetic nephropathy have manifested the risk of this complication, long-term morphologic studies (Mauer, Steffes, Goetz, unpublished data) indicate that at 6–10 yr posttransplant, some diabetic patients have few or no mesangial lesions while others have advanced mesangial changes. One explanation is that there are unique characteristics intrinsic to the glomerulus that determine the rate at which the pathologic response to the diabetic state develops. Relationships of susceptibility to diabetic microvascular lesions and histocompatibility antigens are weak or nonexistent.[39,40] Identification of a cohort of IDDM patients protected from secondary complications could open important avenues of research into the pathogenesis of secondary complications. However, it is impossible at present to identify these individuals with certainty without morphologic confirmation of their protected status since advanced renal lesions of diabetes can be present without clinical warning signals.

We conclude, therefore, that the study of diabetic nephropathy would be markedly enhanced by carefully designed and executed studies of renal biopsy tissues of IDDM

patients. Progress in understanding pathogenetic mechanisms and in solving the crucial issues regarding the effects of improved metabolic control on diabetic nephropathy will be greatly facilitated by combined analyses of renal structural and functional parameters. It is hoped that this single most common cause of kidney failure in the Western world does not continue to be so veiled in mystery because of misunderstandings of the natural history of diabetic nephropathy and of the risks of the renal biopsy procedure.

ACKNOWLEDGMENTS

We thank Cindy Dawis for typing the manuscript. This work was supported in part by NIH grant AM16797, the Juvenile Diabetes Foundation, and the Minnesota Medical Foundation.

REFERENCES

[1] Mauer, S. M., Steffes, M. W., and Brown, D. M.: The kidney in diabetes. Am. J. Med. 1981; 70:603–12.

[2] Jones, R. H., Hayakawa, H., Mackay, J. D., Parsons, V., and Watkins, P. J.: Progression of diabetic nephropathy. Lancet 1979; 1:1105–1106.

[3] Parving, H. H., Smidt, U. M., Frusberg, B., Bonnevie-Nielsen, V., and Anderson, A. R.: A prospective study of glomerular filtration rate and arterial blood pressure in insulin-dependent diabetics with diabetic nephropathy. Diabetologia 1981; 20:457–61.

[4] Burkholder, P. M.: Atlas of Human Glomerular Pathology. Hagerstown, Harper and Row, 1974:325–29.

[5] Hostetter, T. H., Troy, J. L., and Brenner, B. M.: Glomerular hemodynamics in experimental diabetes. Kidney Int. 1981; 19:410–15.

[6] Mogensen, C. E.: Renal function changes in diabetes. Diabetes 1976; 25 (Suppl. 2):872–79.

[7] Viberti, G. C., Pickup, J. C., Jarrett, R. J., and Keen, H.: Effect of control of blood glucose on urinary excretion of albumin and B2-microglobulin in insulin-dependent diabetes. N. Engl. J. Med. 1979; 300:638–41.

[8] Azar, S., Johnson, M. A., Hentel, B., and Tobian, L.: Single nephron pressures, flows and resistances in hypertensive kidneys. Kidney Int. 1977; 12:28–40.

[9] Olson, J. L., Hostetter, T. H., Rennke, H. G., Venkatachalam, M. A., and Brenner, B. M.: Mechanisms of altered glomerular permselectivity and progressive glomerulosclerosis following extreme ablation of renal mass. In press. Kidney Int.

[10] Steffes, M. W., Brown, D. M., and Mauer, S. M.: Diabetic glomerulopathy following unilateral nephrectomy in the rat. Diabetes 1978; 27:35–41.

[11] Hägg, E.: Influence of insulin treatment on glomerular changes in rats with longstanding alloxan diabetes. Acta Pathol. Microbiol. Scand. 1974; 82:228–36.

[12] Mauer, S. M., Steffes, M. W., Azar, S., Sandberg, S., and Brown, D. M.: The effects of Goldblatt hypertension on development of glomerular lesions of diabetes mellitus in the rat. Diabetes 1978; 27:738–44.

[13] Steffes, M. W., Buchwald, H., Wigness, B. D., Groppoli, T. J., Rupp, W. M., Rohde, T. D., Blackshear, P. J., and Mauer, S. M.: Diabetic nephropathy in the uninephrectomized dog. Microscopic lesions after one year. Kidney Int. 1982; 21:721–24.

[14] Mogensen, C. E.: Diabetes mellitus and the kidney. Kidney Int. 1982; 21:673–75.

[15] Christiansen, J. S., Gammelgaard, J., Tronier, B., Svendsen, P. A., and Parving, H. H.: Kidney function and size in diabetic before and during initial insulin treatment. Kidney Int. 1982; 21:683–88.

[16] Mauer, S. M., Steffes, M. W., Sutherland, D. E. R., Brown, D. M., and Goetz, F. C.: Structural-functional relationships in diabetic nephropathy. Manuscript submitted. J. Clin. Invest. 1982.

[17] Gellman, D. D., Pirani, C. L., Soothill, J. F., Muehrcke, R. C., Maduros, W., and Kark, R. M.: Structure and function in diabetic nephropathy. The importance of diffuse glomerulosclerosis. Diabetes 1959; 8:251–56.

[18] Hostetter, T. H., Olson, J. L., Rennke, H. G., Venkatachalam, M. A., and Brenner, B. M.: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am. J. Physiol. 1981; 24:F85–93.

[19] Mitch, W. E., Walser, M., Buffington, C. A., and Lemann, J.: A simple method for estimating progression of chronic renal failure. Lancet 1976; 2:1326–28.

[20] Rutherford, W. E., Blondin, J., Miller, J. P., Greenwalt, A. S., and Vaura, J. D.: Chronic progressive renal disease: rate of change of serum creatinine. Kidney Int. 1977; 11:62–70.

[21] Mogensen, C. E.: Progression of nephropathy in long-term diabetics with proteinuria and effect of initial anti-hypertensive treatment. Scand. J. Clin. Lab. Invest. 1976; 36:383–88.

[22] Olson, J. L., Hostetter, T. H., Rennke, H. G., Venkatachalam, M. A., and Brenner, B. M.: Mechanisms of altered glomerular permselectivity and progressive glomerulosclerosis following extreme ablation of renal mass. In press. Kidney Int.

[23] Carrie, B. J., and Myers, B. D.: Proteinuria and functional characteristics of the glomerular barrier in diabetic nephropathy. Kidney Int. 1980; 17:667–76.

[24] Winetz, J. A., Golbertz, H. B., Spencer, R. J., Adee, J., and Myers, B. D.: Glomerular function in advanced human diabetic nephropathy. Kidney Int. 1982; 21:750–56.

[25] Gundersen, H. J. G., and Østerby, R.: Glomerular size and structure in diabetes mellitus. II. Late abnormalities. Diabetologia 1977; 13:43–48.

[26] Viberti, G., Mackintosh, D., Bilous, R. W., Pickup, J. C., and Keen, H.: The proteinuria of diabetes mellitus. The role of spontaneous and experimental variation of glycaemia. Kidney Int. 1982; 21:714–20.

[27] Purkenson, M. L., Hoffsten, P. E., and Klahr, S.: Pathogenesis of the glomerulopathy associated with renal infarction in rats. Kidney Int. 1976; 9:407–17.

[28] Knowles, H. C., Guest, G. M., and Lampe, J.: The course of juvenile diabetes treated with measured diet. Diabetes 1975; 24:239–73.

[29] Deckert, T., Poulsen, J., and Larsen, M.: Prognosis in juvenile diabetes. Acta Endocrinol. 1976; 203 (Suppl. 82):15.

[30] Unger, R. H.: Meticulous control of diabetes: benefits, risks, and precautions. Diabetes 1982; 31:479–84.

[31] McMillan, D. E., Utterback, N. G., and La Puma, J.: Reduced erythrocyte deformability in diabetes. Diabetes 1978; 27:895–99.

[32] Bern, M. M.: Platelet functions in diabetes mellitus. Diabetes 1978; 27:342–46.

[33] Siperstein, M. D., Unger, R. H., and Madison, L. L.: Studies of muscle capillary basement membranes in normal subjects, diabetic and pre-diabetic patients. J. Clin. Invest. 1968; 47:1973–98.

[34] Gundersen, H. J. G., Østerby, R., and Lundbaek, K.: The basement membrane controversy. Diabetologia 1978; 15:361–64.

[35] Siperstein, M. D., Feingold, K. R., and Bennett, P. H.: Hyperglycemia and diabetic microangiopathy. Diabetologia 1978; 14:365–68.

[36] Williamson, J. R., and Kilo, C.: A common sense approach resolves the basement controversy and the NIH Pima Indian Study. Diabetologia 1979; 17:129–32.

[37] Mauer, S. M., Barbosa, J., Vernier, R. L, Kjellstrand, C. M., Buselmeier, T. J., Simmons, R. L., Najarian, J. S., and Goetz, F. C.: Development of diabetic vascular lesions in normal kidneys transplanted into patients with diabetes mellitus. N. Engl. J. Med. 1976; 295:916–20.

[38] Mauer, S. M., Miller, K., Goetz, F. C., Barbosa, J., Simmons, R. L., Najarian, J. S., and Michael, A. F.: Immunopathology of renal extracellular membrane in kidneys transplanted into patients with diabetes mellitus. Diabetes 1976; 25:709–12.

[39] Bodansky, H. V., Wolf, E., Cudworth, A. Cr., Dean, B. M., Nineham, L. J., Bottazzo, J. R., Matthews, J. A., Kurtz, A. B., and Kohner, E. M.: Genetic and immunologic factors in microvascular disease in type I insulin-dependent diabetes. Diabetes 1982; 31:70–74.

[40] Barbosa, J.: Is diabetic microangiopathy genetically heterogeneous? HLA and diabetic nephropathy. Horm. Metab. Res. 1981; 11 (Suppl.):77–80.