Diabetologia (1981) 21: 89–93

Diabetologia



*Review Articles*

# Functional and Morphological Renal Manifestations in Diabetes Mellitus

C. E. Mogensen, M. W. Steffes, T. Deckert and J. Sandahl Christiansen

Second University Clinic of Internal Medicine, Municipal Hospital, Aarhus, Denmark
Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota, USA, and Steno Memorial Hospital, Gentofte, Denmark

Diabetic nephropathy presents the most serious complication to the patient with young onset insulin-dependent (Type 1) diabetes mellitus. It develops in approximately 30–35% of such patients [1] and signifies a grave prognosis [2].

## Early Functional Changes in the Diabetic Kidney

Abnormal renal function, including elevated glomerular filtration rate (GFR) [3–5] and increased renal plasma flow (RPF) [6, 7] can be demonstrated in diabetic man very early in the disease, even at the time of diagnosis. Increased GFR is invariably found and usually remains at an elevated level in the diabetic until the development of proteinuria [8, 9], while the enhancement of RPF does not always reach statistical significance [7, 9]. The elevated GFR in diabetes mellitus [10, 11] may reflect changes in any of several determinants of GFR: 1) RPF, 2) the colloid osmotic pressure within the glomerular capillaries, 3) the transglomerular hydraulic pressure and 4) the effective hydraulic ultrafiltration coefficient (kf) which is determined by the hydraulic conductance and glomerular surface area [12].

Haemodynamic factors, such as increased RPF [6, 7, 13, 14] and increased hydraulic pressure [13, 14], most likely contribute to the elevated GFR. Micropuncture studies in moderately diabetic Munich Wistar rats have revealed increased GFR, RPF, increased single nephron GFR and increased intraglomerular capillary pressure [13]. These findings have been confirmed in another rat strain [14]. However, in that study the increased hydraulic pressure gradient resulted from decreased proximal tubular pressure.

There are no data on hydraulic conductance of the glomerular membrane in diabetes, but changes in glomerular capillary surface area are very likely to contribute to alterations in renal function in diabetic patients [10].

The morphological alterations which are seen in diabetic kidneys early in the disease include a substantial increase in kidney volume [7, 15] for the most part representing an increase in renal tubular volume [16]. In addition the glomeruli increase in volume [17] resulting in an increased peripheral capillary surface area of the glomeruli [18]. The latter might produce an elevation of kf and thus contribute significantly to the elevated GFR in diabetes.

To what extent each of the observed morphological and functional alterations contributes to the increased GFR remains to be clarified. Rapid reversal of elevated GFR, induced by improved metabolic control [4, 19, 20] without concomitant changes in glomerular volume [18], points towards haemodynamic changes being the major determinants of the increased GFR. However, other observations implicate morphological changes. These include the finding that short periods (one week) of strict metabolic control fail to normalize completely GFR [20]. Also GFR correlates closely with the glomerular capillary surface area [21].

The biochemical or hormonal pertubations leading to increased GFR represent complex interactions. Glucose and/or its metabolites seem to be important factors in the elevation of GFR and RPF [22–24], but the actual causative mechanisms have yet to be elucidated. Possibly an increased tubular reabsorption of glucose combined with altered reabsorption of electrolytes, phosphate and water may influence glomerular function [25]. Glucagon [26] and growth hormone [27, and Christiansen et al., unpublished data] have been shown to induce small but significant increments of RPF and GFR. Other hormones, such as prostaglandins and ACTH, and changes in vascular reactivity to hormonal stimuli must also be considered [28].

0012-186X/81/0021/0089/$01.00

The moderate increases of urinary albumin excretion [29, 30] demonstrated during periods of poor control in recent-onset diabetics most likely differ fundamentally from the very substantial excretion of protein associated with clinical diabetic nephropathy. Since tubular dysfunction does not seem to increase microalbuminuria in periods of poor diabetic control [11], enhanced glomerular filtration of albumin must be the main cause. Microalbuminuria rises during and immediately after physical exercise in insulin – dependent patients and follows an increase of transglomerular passage of albumin [31, 32]. These observations might be explained by altered structure or reactivity of diabetic glomeruli to haemodynamic changes induced by physical exercise [33, 34].

All the functional changes are reversible and can be normalized during periods of excellent control [4, 19, 20, 35]. Nevertheless since most insulin-dependent diabetics are in only fair or sometimes even poor metabolic control, cross-sectional studies of patients without obvious complications have revealed elevated GFR and sometimes increased microalbuminuria [4, 35].

## Structural Changes in the Diabetic Kidney

The development of pathological changes in diabetic kidneys has been extensively studied [36, 37]. In man an increase in glomerular basement membrane thickness occurs within the first 2–3 years of diabetes [36], preceding increases in mesangial volume and mesangial basement membrane-like material [36, 38, 39]. These changes follow at a much later time the increases in kidney volume and in glomerular volume seen within the first weeks of diabetes [15, 40].

Most likely these morphological changes represent a response to the metabolic and haemodynamic changes seen in diabetes. Diabetic glomerulopathy can be avoided by strict metabolic control in streptozotocin-diabetic animals [41]. It may be partially reversed following islet transplantation. Increased glomerular volume, increased mesangial volume and mesangial deposition of immunoglobulins all reflecting diabetic renal lesions [42], are ameliorated within two months after islet transplantation in diabetic rats [43]. However, another study also using islet transplantation suggested that some mesangial lesions do not regress after one month of normoglycaemia [44]. In addition incrased glomerular basement membrane thickness remained unchanged following improved diabetic control for as long as six months following islet transplantation [45]. Taken together these observations imply a poor correlation between glomerular basement membrane thickness (resisting reversal with restoration of the normal metabolic state) and other lesions of glomerular pathology in the diabetic rat which do respond to therapy.

Exposure of the diabetic glomeruli to incrased flow and to increased capillary pressure putatively accelerates the development of diabetic glomerulopathy [46–49]. Observations in man and animals with unilateral renal artery stenosis suggest the role of increased glomerular capillary pressure in accelerating diabetic glomerulopathy [46, 48]. On the other hand, kidneys which are protected against increased flow and pressures (in fact exposed to very low flows and pressures), will still demonstrate diabetic renal disease, emphasizing that the metabolic consequences of diabetes are themselves fundamental factors in the pathogenesis of diabetic kidney disease.

Light microscopy can demonstrate glomerular sclerosis in nearly all Type 1 (insulin dependent) diabetic patients after several years of diabetes [50]. Why only some patients experience progressive glomerular sclerosis with the development of end-stage renal failure remains an important question. The sclerotic alterations of the mesangium seem to fill the glomeruli to such an extent that they can no longer function. The correlation between sclerotic, occluded glomeruli and the demise of renal function strongly implies that the continued destruction and consequent dysfunction of glomeruli lead to end-stage diabetic glomerulopathy [51]. There are some patients however, who may have substantial glomerular pathology and yet seem able to maintain normal renal function [50]. Understanding why this subset of patients resists end-stage renal disease may provide important insights into preventing the renal complications of diabetes mellitus.

## Toward Understanding Clinical Diabetic Nephropathy

Diabetic nephropathy may be defined clinically as an increase in urinary protein excretion to levels persistently above 0.5 g/24 h in diabetics without cardiac insufficiency or renal tract infection [1]. Those patients who develop clinical diabetic nephropathy have a poor prognosis [52, 53]. Approximately 50% will die within 7 years after onset of proteinuria, and in the remainder impaired renal function will proceed inexorably [52, 54]. The causes of death in insulin dependent patients suffering from diabetic nephropathy include uraemia (80%), myocardial infarction (10%), and 10% due to other causes [1].

About 30% of young onset insulin dependent diabetics will develop persistent proteinuria [1]. The remainder may never develop this complication

despite very long duration of disease [1]. The risk of developing diabetic nephropathy in insulin dependent diabetics has been shown to be significantly higher in males than in females, and significantly higher in diabetics with onset between 0–10 years of age, than in diabetics with onset of diabetes between 11 and 30 years of age [52]. Genetic factors may in part explain these differences. In insulin independent diabetics the genetic trait of chlorpropamide-induced alcohol flushing seems to protect against the development of diabetic nephropathy [55].

It is not known why some insulin dependent diabetics gradually increase the urinary albumin excretion from normal or microalbuminuric levels to gross proteinuria, or why persisting glomerular hyperfunction in such cases changes to a rapid decline in GFR. The incrase in albuminuria does not seem to be preceded by a decrease of GFR [8, 56] nor by an incrase in blood pressure [57]. Newly diagnosed insulin-dependent diabetics may demonstrate a slightly increased blood pressure [58], but this increase is difficult to demonstrate later in the disease. Not until the development of clinical diabetic nephropathy does blood pressure begin to increase significantly and seem to serve as an accelerating factor in the progression of diabetic nephropathy. Thus blood pressure per se does not seem to be responsible for the development of diabetic nephropathy, but might well contribute to the progression of the kidney disease [56]. Furthermore, effective antihypertensive treatment may help to ameliorate the progression of diabetic nephropathy [59].

It has been suggested that insulin dependent diabetes may cause a severely increased rigidity of the walls of the intralobular renal arterioles, impairing their ability to change calibre, e. g. during vigorous exercise [60]. These defects could lead to incrased vessel wall stress increasing protein entry into the walls of small arterioles and enhancing connective tissue synthesis. The response may be similar to that seen in hypertension or to changes occurring following mechanical endothelial damage. Increased intralobular arteriosclerosis has been found in diabetics with renal insufficiency compared with diabetics with glomerulosclerosis but without renal failure [60]. The loss of tone in renal arteries may impair their ability to protect the glomeruli from elevated pressures. If so, the consequent exposure of diabetic glomeruli to incrased intracapillary pressure may accelerate their destruction. This hypothesis underlines the importance of haemodynamic factors in the pathogenesis of diabetic nephropathy [46, 48].

Another explantation for the rather sudden incrase of microalbuminuria to the level of gross proteinuria in some insulin-dependent diabetics might include a specific change of the glumerular barrier-function in these patients [61]. An increased size of gap junctions or pores in glomerular capillary walls, however, has not been found. On the other hand, loss of perm-selectivity properties of the glomerular capillary wall, and impaired shape-discrimination for large molecules in diabetics with nephrotic syndrome and severely reduced GFR have been described [61]. Foot process degeneration with detachment of epithelial cells and denudation of the underlying glomerular basement membrane, recently described in advanced diabetic nephropathy, may provide the structural basis for this pehnomenon [62]. More extensive physiological and morphological studies are desirable in order to clarify further if the functional and morphological changes found early in Type 1 (insulin dependent) diabetes have a causal relationship to the late development of clinical diabetic nephropathy.

## Prevention and Reversal of Diabetic Renal Alterations

As alluded to above, the early alterations in GFR, RPF, renal size, mesangial mass and urinary loss of albumin remain amenable to normalization with improved control of the diabetic state. The point at which these alterations become unresponsive to treatment has not been determined in man. The evidence from experiments in rats emphasizes the resilience of the diabetic kidney in that substantial amelioration of diabetic renal lesions can be achieved with improved diabetic control [43]. However, reversal of the renal pathology of diabetes mellitus in man has not been demonstrated. Similar studies in man which demonstrate that good control can prevent the renal lesions are still lacking. Until now, excellent regulation of blood glucose by subcutaneous insulin infusion has not significantly reduced the protein excretion in patients with diabetic nephropathy [34], and therefore the question whether good metabolic control will prevent diabetic nephropathy in insulin dependent diabetes has yet to be solved. Epidemiological studies [63] lend support to the concept that metabolic control does correlate with the development of proteinuria. However, additional efforts must be directed towards the expansion of such studies in man.

*Acknowledgement.* The present review embraces the contributions and discussions of a symposium "The kidney in diabetes – towards understanding diabetic nephropathy", which was held at the Steno Memorial Hospital, Copenhagen, 18–19 September 1980.

## References


1. Deckert T, Andersen AR, Christiansen JS, Andersen JK (1981) Course of diabetic nephropathy. Factors related to development. Acta Endocrinol 97 (Suppl 242): 14–15
2. Andersen AR, Andersen JK, Christiansen JS, Deckert T (1978) Prognosis for juvenile diabetics with nephropathy and failing renal function. Acta Med Scand 203: 131–134
3. Stalder G, Schmid R, Wolff MV (1960) Funktionelle Mikroangiopathie der Nieren beim behandelten Diabetes Mellitus im Kindesalter. Dtsch Med Wochenschr 85: 346–350
4. Mogensen CE (1972) Kidney function and glomerular permeability to macromolecules in juvenile diabetes. Dan Med Bull 19 (Suppl 3): 1–40
5. Ditzel J, Junker K (1972) Abnormal glomerular filtration rate, renal plasma flow and renal protein excretion in recent and short-term diabetes. Br Med J II: 13–19
6. Mogensen CE (1971) Glomerular filtration rate and renal plasma flow in short-term and long-term juvenile diabetes mellitus. Scand J Clin Lab Invest 28: 91–100
7. Christiansen JS, Gammelgaard J, Frandsen M, Parving H-H (1981) Increased kidney size, glomerular filtration rate and renal plasma flow in short-term insulin-dependent diabetics. Diabetologia 20: 451–456
8. Mogensen CE (1976) Progression of nephropathy in long-term diabetics with proteinuria and effect of initial antihypertensive treatment. Scand J Clin Lab Invest 36: 383–388
9. Mogensen CE (1972) Glomerular filtration rate and renal plasma flow in long-term juvenile diabetics without proteinuria. Br Med J 4: 257–259
10. Mogensen CE, Østerby R, Gundersen HJG (1979) Early functional and morphologic vascular renal consequences of the diabetic state. Diabetologia 17: 71–76
11. Viberti GC (1979) Early functional and morphological changes in diabetic nephropathy. Clin Nephrol 12: 47–53
12. Brenner BM, Humes HD (1977) Mechanisms of glomerular ultrafiltration. N Engl J Med 297: 148–154
13. Hostetter TH (1981) Renal microcirculation in diabetes mellitus. Acta Endocrinol 97 (Suppl 242): 22–24
14. Jensen PK, Christiansen J Sandahl, Steven K, Parving H-H (1981) Renal function in diabetic rats. Acta Endocrinol 97 (Suppl 242): 25
15. Mogensen CE, Andersen MJF (1973) Increased kidney size and glomerular filtration rate in early juvenile diabetes. Diabetes 22: 706–712
16. Seyer-Hansen K, Hansen J, Gundersen HJG (1980) Renal hypertrophy in experimental diabetes. Diabetologia 18: 501–505
17. Østerby R, Gundersen HJG (1975) Glomerular size and structure in diabetes mellitus. Early abnormalities. Diabetologia 11: 225–229
18. Kroustrup JP, Gundersen HJG, Østerby R (1977) Glomerular size and structure in diabetes mellitus. III. Early enlargement of the capillary surface. Diabetologia 13: 207–210
19. Parving H-H, Rutili F, Granath K, Noer I, Deckert T, Lyngsøe J, Lassen NA (1979) Effect of metabolic regulation on renal Leakiness to Dextran molecules in short-term insulin-dependent diabetics. Diabetologia 17: 157–160
20. Christiansen J Sandahl, Frandsen M, Svendsen P Aaby, Gammelgaard J, Parving H-H (1981) Rapid changes in kidney function – factors influencing kidney function in diabetics and normal man. Acta Endocrinol 97 (Suppl 242): 11–14
21. Hirose K, Tsuchida H, Østerby R, Gundersen HJG (1980) A strong correlation between glomerular filtration rate and filtration surface in diabetic kidney hyperfunction. Lab Invest 43: 434–437
22. Brøchner-Mortensen J (1973) The glomerular filtration rate during moderate hyperglycemia in normal man. Acta Med Scand 194: 31–37
23. Fox M, Thier S, Rosenberg L, Segal S (1964) Impaired renal tubular function induced by sugar infusion in man. J Clin Endocrinol Metab 24: 1318–1322
24. Christiansen J Sandahl, Frandsen M, Parving H-H (1981) Effect of intravenous glucose infusion on renal function in normal man and in insulin-dependent diabetics. Diabetologia (In press)
25. Ditzel, J, Brøchner-Mortensen J, Rødbro P (1981) A combined disturbance in renal tubular handling of glucose and phosphate leads to increased glomerular filtration rate in diabetes mellitus. Acta Endocrinol 97 (Suppl 242): 16–18
26. Parving H-H, Christiansen J Sandahl, Noer I, Tronier B, Mogensen CE (1980) The effect of glucagon infusion of kidney function in short-term insulin-dependent juvenile diabetics. Diabetologia 19: 350–354
27. Corvilain J, Abramow M (1962) Some effects of human growth hormone on renal hemodynamics and on tubular transport in man. J Clin Invest 41: 1230–1235
28. Stephan F, Reville P, de Laharpe F (1981) Effect of hormonal and nutritional factors on kidney size and renal compensation hypertrophy. Acta Endocrinol 97 (Suppl 242): 51–52
29. Keen H, Clouverakis C (1963) An immunoassay method for urinary albumin at low concentrations. Lancet 2: 913–916
30. Miles DW, Mogensen CE, Gundersen HJG (1970) Radio immunoassay for urinary albumin using a single antibody. Scand J Clin Lab Invest 26: 5–11
31. Viberti GC, Jarrett RJ, McCartney M, Keen H (1978) Increased glomerular permeability to albumin induced by exercise in diabetic subjects. Diabetologia 14: 293–300
32. Mogensen CE, Vittinghus E (1975) Urinary albumin excretion during exercise in juvenile diabetics. Scand J Clin Lab Invest 35: 295–300
33. Vittinghus E, Mogensen CE (1981) Albumin excretion during physical exercise in diabetes. Studies on the effect of insulin treatment and of the renal hemodynamic response. Acta Endocrinol 97 (Suppl 242): 61–62
34. Viberti GC, Keen H, Pickup JC, Bilous RW (1981) Proteinuria and diabetic control in insulin-dependent diabetes mellitus. Acta Endocrinol 97 (Suppl 242): 59–60
35. Viberti GC, Pickup JC, Jarrett RJ, Keen H (1979) Effect of control of blood glucose on urinary excretion of albumin and β-2-microglobulin in insulin-dependent diabetes. N Engl J Med 300: 638–641
36. Østerby R (1975) Early phases in the development of diabetic glomerulopathy. A quantitative electron microscopic study. Acta Med Scand 200 (Suppl 574): 1–82
37. Steffes MW, Brown DM, Mauer SM (1979) The development, enhancement, and reversal of the secondary complications of diabetes mellitus. Human Pathol 10: 293–299
38. Iridaka K, McCoy J, Kimmelstiel P (1968) The glomerular mesangium, a qualitative analysis. Lab Invest 19: 573–578
39. Mauer SM, Michael AF, Fish AJ, Brown DM (1972) Spontaneous immunoglobulin and complement deposition in glomeruli of diabetic rats. Lab Invest 19: 573–579
40. Gundersen HJG, Hirose K, Kroustrup JP, Seyer-Hansen K, Østerby R (1981) Early structural changes in glomerular capillaries. Acta Endocrinol 97 (Suppl 242): 19–21
41. Rasch R (1981) Functional and structural abnormalities in the kidneys of IDDM – studies on the prevention of glomerulopathy in diabetic rats. Acta Endocrinol 97 (Suppl 242): 43–44
42. Westberg NG (1980) Diabetic nephropathy. Pathogenesis and prevention. Acta Endocrinol 94 (Suppl 238): 85–101
43. Mauer SM, Steffes MW, Sutherland DER, Najarian JS, Michael AF, Brown DM (1975) Studies on the rate of regres-

sion of the glomerular lesions in diabetic rats treated with pancreatic islet transplantation. Diabetes 24: 280–284
44. Gøtzsche O, Gundersen HJG, Østerby R (1979) Reversibility and non-reversibility of renal morphological changes in early experimental diabetes after pancreatic transplantation. Acta Endocrinol 96 (Suppl 227): 27–28
45. Steffes MW, Brown DM, Basgen JM, Matas AJ, Mauer SM (1979) Glomerular basement membrane thickness following islet transplantation in the diabetic rat. Lab Invest 41: 116–118
46. Mauer SM, Steffes MW, Azar S, Sandberg SK, Brown DM (1978) The effect of Goldblatt hypertension on the development of glomerular lesions of diabetes mellitus in the rat. Diabetes 27: 738–744
47. Steffes MW, Brown DM, Mauer SM (1978) Diabetic glomerulopathy following unilateral nephrectomy in the rat. Diabetes 27: 25–32
48. Berkman J, Rifkin H (1974) Unilateral nodular diabetic glomerulosclerosis (Kimmelstiel-Wilson): Report of a case. Metab Clin Exp 22: 715–718
49. Brenner BM. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA (1981) The role of glomerular hyperfiltration in the initiation and progression of diabetic nephropathy. Acta Endocrinol 97 (Suppl 242): 7–10
50. Thomsen AChr (1965) The kidney in diabetes mellitus. PhD thesis, Munksgaard, Copenhagen
51. Østerby R, Gøtzsche O, Gundersen HJG, Hirose K, Lundbaek K, Seyer-Hansen K (1981) Progression of glomerular structural kidney alterations in diabetic rat and man. Acta Endocrinol 97 (Suppl 242): 63–64
52. Christiansen JS, Andersen AR, Andersen JK, Deckert T (1981) Diabetic nephropathy – prognosis and factors related to development. In: Irsigler K, Kunz KM, Owens DR, Regal H (eds) New approaches to insulin therapy. MTP Press, Lancaster. (In press)
53. Kussman MJ, Goldstein HH, Ray EG (1974) Clinical course of diabetic nephropathy. Diabetes 23: 357–362
54. Jones RH, Mackay JD, Hayakawa H, Parsons V, Watkins PJ (1979) Progression of diabetic nephropathy. Lancet 1: 1105–1106
55. Barnett AH, Leslie RDG, Pyke DA (1981) Chlorpropamide-alcohol flushing and proteinuria in non-insulin dependent diabetes. Br Med J 282: 522–523
56. Parving H-H, Andersen AR, Smidt U, Friisberg B, Bonnevie-Nielsen V, Svendsen PAa (1981) The natural course of glomerular filtration rate and arterial blood pressure in diabetic nephropathy, and the effect of antihypertensive treatment. Acta Endocrinol 97 (Suppl 242): 39–40
57. Deckert T, Poulsen JE (1981) Diabetic nephropathy. Fault or destiny? Diabetologia (In press)
58. Keen H, Chlouverakis C, Fuller J, Jarrett RJ (1969) The concomitants of raised blood sugar: Studies in newly-detected hyperglycaemics. Guy's Hospital Reports 118: 247–254
59. Mogensen CE (1980) Antihypertensive treatment inhibiting the progression of diabetic nephropathy. Acta Endocrinol 94 (Suppl 238): 102–111
60. McMillan D (1981) Renal vascular changes in diabetes and their predicted effects. Acta Endocrinol 97 (Suppl 242): 26–28
61. Carrie BJ, Myers BD, Golbetz AB (1980) Proteinuria and functional characteristics of the glomerular barrier in diabetic nephropathy. Kidney Int 17: 669–675
62. Cohen AH, Mampaso F, Zamboui L (1977) Glomerular podocyte degeneration in human renal disease: An ultrastructural study. Lab Invest 37: 40–42
63. Pirart J (1977) Diabète et complications dégénératives. Présentation d'une étude prospective portant sur 4.400 cas observés entre 1947 et 1973 (three parts). Diabète et Métabolisme 3: 97–107, 173–182, 245–256

Received: 13 February 1981

Dr. J. Sandahl Christiansen
Steno Memorial Hospital
DK-2820 Gentofte, Denmark