Prevention of Diabetic Glomerulopathy by Pharmacological Amelioration of Glomerular Capillary Hypertension

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Abstract

Two groups of adult male Munich-Wistar rats and a third group of nondiabetic age-matched and weight-matched normal control rats underwent micropuncture study 1 mo, and morphologic studies 14 mo, after induction of streptozotocin diabetes or sham treatment. All animals were fed standard rat chow. Diabetic rats received daily ultralente insulin to maintain stable moderate hyperglycemia (~350 mg/dl). In addition, one group of diabetic rats was treated with the angiotensin I converting enzyme inhibitor, enalapril, 15 mg/liter of drinking water. Average kidney weight, whole kidney and single-nephron glomerular filtration rate, and glomerular plasma flow rate were elevated to similar values in both groups of diabetic rats, relative to normal control rats. Non-enalapril-treated diabetic rats exhibited significant elevations in mean glomerular capillary hydraulic pressure and transcapillary hydraulic pressure gradient, compared with the other groups studied, and only this group eventually developed marked and progressive albuminuria. Likewise, histological examination of the kidneys at 14 mo disclosed a high incidence of glomerular structural abnormalities only in non-enalapril-treated diabetic rats. These findings indicate that prevention of glomerular capillary hypertension in rats with diabetes mellitus effectively protects against the subsequent development of glomerular structural injury and proteinuria. This protection is afforded despite pronounced hyperglycemia and elevated levels of glucoseylated hemoglobin, further supporting our view that hemodynamic rather than metabolic factors predominate in the pathogenesis of diabetic glomerulopathy.

Introduction

A state of glomerular hyperfiltration has been consistently demonstrated in patients with newly diagnosed insulin-dependent (Type I) diabetes mellitus (DM) (1–4), as well as in the early stages of experimental diabetes in animals (5–7). In the latter, this hyperfiltration has been shown to result from concomitant elevations in glomerular plasma flow rate (QG) and mean glomerular capillary hydraulic pressure (5–7). These early glomerular hemodynamic abnormalities have been implicated in the pathogenesis of the glomerulopathy that eventually develops in this disorder (8, 9). We have shown previously (7) that in rats with diabetes induced by streptozotocin (STZ), dietary protein restriction limits both early elevations in glomerular pressures and flows and the subsequent development of glomerular structural injury. Moreover, glomerular structural injury can be effectively prevented despite pronounced hyperglycemia as long as glomerular pressures and flows are maintained within normal limits. These findings provide strong evidence that hemodynamic, rather than metabolic, factors play a fundamental role in the initiation and progression of diabetic glomerulopathy.

Limitation of glomerular hemodynamic alterations has also been shown to prevent glomerular injury in rats subjected to severe renal ablation. Hostetter and co-workers (10) showed that dietary protein restriction normalizes glomerular hemodynamics and completely arrests glomerular injury in rats following 11/12 renal ablation. More recently, Anderson and co-workers (11), using rats with 5/6 renal ablation, demonstrated that treatment with the potent angiotensin I converting enzyme inhibitor, enalapril, not only restores systemic arterial pressure to normal levels but also selectively normalizes mean glomerular capillary hydraulic pressure. 8 wk after renal ablation, enalapril-treated rats exhibited a striking attenuation of glomerular structural injury, thus strengthening the possibility that glomerular hemodynamic abnormalities, and in particular elevations in glomerular pressures, also play a key role in the pathogenesis of diabetic glomerulopathy.

Systemic hypertension has been demonstrated to worsen, while antihypertensive therapy ameliorates, the progression of established diabetic glomerulopathy (12–14). However, administration of antihypertensive therapy to normotensive diabetic patients has never been attempted as a prophylactic measure against glomerular disease. Since the kidneys of diabetic subjects exhibit marked vasodilatation, it seems likely that even slight reductions in systemic arterial pressure would reduce glomerular.

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1. Abbreviations used in this paper: ΔP, glomerular transcapillary hydraulic pressure difference; sG, systemic plasma colloid osmotic pressure.


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Pathophysiology of Diabetic Glomerulopathy 1925
capillary hydraulic pressure and thereby prevent the subsequent
development of glomerular injury in this model, even in the
setting of pronounced and longstanding hyperglycemia. Ac-
cordingly, the present study was undertaken to test this hypo-
thesis and to dissociate the specific deleterious effects of hemo-
dynamic abnormalities from any hypothetical effects of deranged
metabolism per se.

Methods

We used 57 adult male Munich-Wistar rats in this study. 39 rats were
made diabetic by a single i.v. injection of STZ (60 mg/kg) under light
anesthesia. Morning glucose concentration was determined biweekly on
all tail blood samples with a reflectance meter (Miles Ames Div., Miles
Laboratories, Inc., Elkhart, IN). Rats received daily evening injections
of a heat-treated ultralente insulin (NOVO Industrie, Copenhagen, Den-
mark) (7, 15), individually adjusted to maintain blood glucose concen-
tration between 200 and 400 mg/dl. Daily insulin dose averaged ~0.8
U. Normal control rats matched for initial age and weight were also
studied. 3–7 d after STZ injection, diabetic rats were randomly assigned
to either of two groups: (a) DM, rats receiving no other therapy than
exogenous insulin, and (b) DM+E, insulin-treated rats also receiving
enalapril (Merck, Sharp, and Dohme, West Point, PA), 15 mg/liter in
the drinking water.

16 diabetic rats and 7 control rats underwent micropuncture study
4–6 wk after STZ injection. Blood glucose concentration was measured
shortly before the experiment and a few rats with values below 200 mg/dl were excluded from micropuncture study. Ad-
ditional determinations made throughout the duration of these studies
verified the persistence of moderate hyperglycemia (300–400 mg/dl).
Rats were anesthetized with Inactin (100 mg/kg) and prepared for mi-
cropuncture as described previously (16). To replace plasma losses as-
associated with anesthesia and surgery (17), isoncotic homologous plasma
obtained from normal rats, equivalent to 1% body weight in volume,
was infused over 50–60 min, followed by a sustaining infusion of 0.8–
1.0 ml/h throughout the rest of the experiment. Inulin, 10 g/100 ml in
normal saline, was also infused at a rate of 1.2 ml/h. Samples of tubule
fluid were obtained from superficial proximal tubules for determinations
of flow rate and inulin concentration. The latter was measured by the
method of Vurek and Pegram (18). Blood samples were obtained from
surface efferent arterioles for determination of total protein concentra-
tion as described previously (16, 19). Hydraulic pressures were measured in
superficial cortical tubules and microvessels by the servo-null technique
(16). Details of the calculations employed are given elsewhere (16).

Rats in each group not subjected to micropuncture study were main-
tained at similar stable levels of moderate hyperglycemia by daily ultra-
lente insulin treatment for 14 mo after induction of diabetes. 24-h urinary
albumin excretion rates were determined at alternate monthly intervals
by the single radial immunodiffusion technique (20). Systolic blood pres-
sures were also measured by tail cuff (TPB) at biweekly intervals in these
conscious rats. At the end of this 14-mo period, rats were anesthetized
with nembutal (50 mg/kg i.p.) and 150 µl of blood were collected for
determination of glycosylated hemoglobin levels (21). Kidneys were then
fixed by perfusion at the measured arterial pressure for 2–3 min with
1.25% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.4).

Morphology. After perfusion fixation, the weight of the left kidney
was recorded and two midcoronal slices of tissue, 2–3-mm thick, were
processed for light microscopic examination. 3-µm-thick paraffin sections
were stained with hematoxylin and eosin and by the periodic acid Schiff
(PAS) reaction. The extent of the glomerular damage was determined
on PAS-stained slides by counting on two sections all glomerular profiles
with segmental or global collapse of capillaries with or without associated
hyalin deposition and adhesion of the tuft to Bowman’s capsule. The
number of glomeruli with segmental or global obsolescence of capillaries
was expressed as a percentage of all glomerular profiles counted in the
histologic sections. Structural alterations at the level of the tubules, inter-
stitium, and blood vessels were assessed qualitatively.

Statistics. Statistical analysis was performed by one-way analysis of
variance followed by Bonferroni’s procedure for multiple pairwise comp-
parisons (22).

Results

Micropuncture experiments. Values for systemic hemodynamic and
whole kidney function 4–6 wk after STZ injection are presented in Table I (mean±1 SEM). Both enalapril-treated
(DM+E) and untreated (DM) diabetic rats exhibited body
weights nearly identical to those of normal control rats. Blood
glucose concentration determined immediately before micro-
puncture was moderately elevated as compared with controls
(87±3 mg/dl) in both DM (350±11 mg/dl) and DM+E (346±14
mg/dl) rats. Systolic blood pressure determined directly from
the femoral artery (SBP) at the time of the experiment was similar
in control (C) and DM rats and did not differ from previously
measured awake tail-cuff blood pressures (TPB) in either group
(Fig. 1). A 20-mmHg reduction in average SBP relative to C or

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight</th>
<th>LKW</th>
<th>BG</th>
<th>TBP</th>
<th>SBP</th>
<th>AP</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (n = 7 rats)</td>
<td>291±7</td>
<td>1.09±0.03</td>
<td>87±3</td>
<td>137±4</td>
<td>147±4</td>
<td>119±3</td>
<td>1.34±0.07</td>
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<tr>
<td>DM (n = 8)</td>
<td>280±6</td>
<td>1.47±0.04*</td>
<td>350±11*</td>
<td>138±5</td>
<td>139±3</td>
<td>117±4</td>
<td>1.84±0.09*</td>
</tr>
<tr>
<td>DM + E (n = 8)</td>
<td>277±3</td>
<td>1.31±0.04*</td>
<td>346±14*</td>
<td>117±3*</td>
<td>124±4*</td>
<td>98±2*</td>
<td>1.58±0.14*</td>
</tr>
</tbody>
</table>

Values given as mean±1 SEM. * P < 0.05 vs. C; † P < 0.05 vs. DM.

Figure 1. Alternate monthly average values for morning blood glucose
concentration and awake systolic blood pressures in untreated and en-
alapril-treated diabetic rats. Blood glucose concentration was main-
tained at stable moderately elevated levels throughout the study in
both groups by daily ultralente insulin treatment. Awake systolic
blood pressures remained persistently lower in enalapril treated rats.
DM values was observed in enalapril-treated (DM+E) rats; once again, values for SBP were similar to previously measured TBP. Mean arterial pressure (AP) was nearly identical in DM and C rats (117±4 mmHg vs. 119±3 mmHg, respectively) while significantly decreased in DM+E rats (98±2 mmHg, P < 0.05).

A marked increase in left kidney weight (LK) was seen in DM rats as compared with controls (1.47±0.04 g vs. 1.09±0.03 g, P < 0.05). Less pronounced renal hypertrophy (1.31±0.04 g) was noted in DM+E rats. A similar pattern was observed with respect to whole-kidney glomerular filtration rate (GFR), with group DM expressing the highest average GFR value, blunted only slightly by enalapril treatment (Table I).

Results concerning glomerular hemodynamics are summarized in Table II and Fig. 2. As with GFR, the average value for single-nerphon glomerular filtration rate (SNFF) was markedly increased in DM rats (81.6±5.7 nl/min vs. 45.9±3.8 nl/min in controls, P < 0.01). This elevation in SNFF was associated with a proportional increase in QA (269±26 nl/min vs. 154±18 nl/min in controls, P < 0.01), hence constancy of single-nerphon filtration fraction, SNFF. Since AP was virtually identical in DM and C groups, the increase in QA must have resulted from renal arteriolar vasodilatation. Afferent (R4), efferent (R5), and total (RT = RA + RE) arteriolar resistances were indeed markedly decreased in DM rats relative to controls. However, the observed fall in RA was more pronounced than in RE, resulting in a decrease in the ratio RA/RE. In consequence, mean glomerular capillary hydraulic pressure (Pgc) and the glomerular transcapillary hydraulic pressure difference (ΔP) were markedly increased in DM rats (63±2 and 52±2 mmHg, respectively, vs. 53±1 and 39±1 mmHg in controls). Since values for the glomerular capillary ultrafiltration coefficient (Kf) (see below) and systemic plasma colloid osmotic pressure (πc) were not significantly different in DM and C groups, the increase in SNFF in DM rats can be attributed to the concomitant elevations observed in QA and ΔP.

Enalapril-treated (DM+E) rats also exhibited a significant increase in LK as compared with controls (1.31±0.04 g vs. 1.09±0.03 g, P < 0.05, Table I). However, this hypertrophy was not as marked as in DM rats (P < 0.05 DM vs. DM+E). GFR and SNFF were numerically, though not significantly, lower in DM+E when compared with DM rats. Since RT in DM+E rats was comparable to the average value obtained in DM rats, and given a moderate reduction in AP, QA was also slightly, but not significantly, diminished in this group relative to DM rats. As a result of the reduction in AP and a slight decrement in RE, ΔP was markedly decreased in DM+E as compared with DM rats; in fact, ΔP achieved complete normalization in DM+E animals (37±1 mmHg vs. 39±1 mmHg in controls). A unique value for Kf could be calculated in every experiment; no significant differences in this parameter were seen among the three groups studied, although DM+E rats tended to have higher values (Table II).

Long-term studies. Results obtained for body weight, LK (after perfusion-fixation with glutaraldehyde), glycylated hemoglobin (HbA1c), and 24-h urinary albumin excretion rate (Uab, V) at 14 mo after induction of diabetes are summarized in Table III. Body weights were moderately lower in DM and DM+E rats as compared with controls. As observed at 4–6 wk of diabetes, LK was markedly increased in DM rats as compared with controls (2.60±0.10 g vs. 1.85±0.10 g, P < 0.05), indicating persistence of renal hypertrophy throughout the study. Renal hypertrophy of slightly lesser magnitude was observed in the DM+E group.

As shown in Fig. 1, a state of stable moderate hyperglycemia was maintained throughout the duration of the experiment in both diabetic groups. That the metabolic derangement was similar in both diabetic groups is further illustrated by the finding in Table III of comparable levels of HbA1c (15.0±0.7% in DM and 12.8±0.3% in DM+E rats, vs. 4.9±0.3% in controls). A moderate but persistent decrease in systolic TBP was observed in DM+E rats throughout the study relative to DM or C values (Fig. 1). Albumin excretion increased with time in DM rats, Uab, V rising on average to 111±22 mg/24 h at 14 mo of diabetes.
Table III. Renal and Systemic Parameters at 14 Mo of Diabetes

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight</th>
<th>LKW</th>
<th>HbA\textsubscript{1}\textsubscript{c}</th>
<th>TBP</th>
<th>U\texttextsubscript{\text{a}} - V</th>
<th>GS</th>
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<tr>
<td></td>
<td>g</td>
<td>g</td>
<td>percent</td>
<td>mmHg</td>
<td>mg/24 h</td>
<td>percent</td>
</tr>
<tr>
<td>C (n = 11 rats)</td>
<td>431±14</td>
<td>1.85±0.10</td>
<td>4.9±0.3</td>
<td>116±2</td>
<td>25±6</td>
<td>1.10±0.18</td>
</tr>
<tr>
<td>DM (n = 13)</td>
<td>355±7*</td>
<td>2.60±0.10*</td>
<td>15.0±0.7*</td>
<td>131±3*</td>
<td>111±22*</td>
<td>6.06±1.20*</td>
</tr>
<tr>
<td>DM + E (n = 10)</td>
<td>328±10*</td>
<td>2.37±0.08*</td>
<td>12.8±0.3*†</td>
<td>109±2‡</td>
<td>18±3‡</td>
<td>0.67±0.20‡</td>
</tr>
</tbody>
</table>

GS, glomerular sclerosis. Values given as mean±1 SEM. * P < 0.05 vs. C; † P < 0.05 vs. DM.

(Fig. 3 and Table III). By contrast, despite a similar degree of stable moderate hyperglycemia, U\textsubscript{\text{a}} - V averaged only 18±3 mg/24 h in DM+E rats at 14 mo, a value similar to that seen in controls (25±6 mg/24 h).

Morphologic findings: A total of 501 glomerular profiles on average were examined and graded per animal. Segmental collapse of the glomerular tuft was observed in over 6% of glomerular profiles at 14 mo in untreated diabetic animals (6.06±1.20). The comparable frequencies of glomerular lesions in enalapril-treated diabetic animals and controls were 0.67±0.20% and 1.10±0.18%, respectively (Table III). Untreated diabetic animals, in addition, showed focal dilatation of proximal convoluted tubules and the presence of occasional casts in the distal segments of the neophron. Focal tubule atrophy with minor nonspecific round cell infiltration and fibrosis of the interstitium was often seen in association with obsolescent glomeruli in this group. In contrast, control animals and enalapril-treated diabetic rats had only minimal disruption of the tubules and interstitium. Vascular changes were not prominent in any of the groups.

Discussion

Sustained hyperfiltration has been demonstrated in early phases of insulin-dependent human diabetes and in animal models, before diabetic microvascular disease has become evident. Hostetter and co-workers (5) showed that this hyperfiltration was the result of concomitant elevations in glomerular plasma flow rate and mean glomerular transcapillary hydraulic pressure difference. Several studies have suggested that these hemodynamic abnormalities are key factors in the initiation and progression of diabetic glomerulopathy (7, 23, 24). Recently, Zatz et al. (7) studied moderately hyperglycemic STZ-diabetic rats 1 and 12 mo after induction of diabetes. Wide variations in glomerular hemodynamics were intentionally induced by feeding diets containing 50, 12, or 6% casein (standard commercial rat chow contains 21–24% protein). Only rats receiving the protein-rich (50%) diet exhibited elevated glomerular pressures and flows at 1 mo of diabetes. Despite comparable metabolic abnormalities in all three diabetic groups, only the group on the highest protein diet developed substantial glomerular injury 12 mo after induction of diabetes. When glomerular hemodynamic abnormalities were attenuated by moderate (12%) or more marked (6%) dietary protein restriction, glomerular structural injury was largely prevented. These studies clearly underscore the importance of early elevation of glomerular pressures and flows in the subsequent development of glomerular injury in this model.

In this study, diabetic rats receiving standard 24% protein chow exhibited glomerular hemodynamic alterations resembling those previously observed in diabetic rats fed a 50% protein diet, and those previously reported by Hostetter et al. (5). As in these previous studies, a marked decrease in glomerular arteriolar resistances, in particular R\textsubscript{A}, was associated with corresponding elevations in Q\textsubscript{A}, ΔP, and SNGFR. In the current study, glomerular hemodynamic alterations were attenuated by converting enzyme inhibition rather than by restricting dietary protein intake. This maneuver has been shown previously in this laboratory (7) to normalize glomerular capillary hydraulic pressure in rats with 5/6 renal ablation, without significantly affecting SNGFR or Q\textsubscript{A}. Unlike rats with severe reduction of renal mass, however, STZ-diabetic rats in the present studies were normotensive or only slightly hypertensive, a finding in keeping with the clinical observation of near-normal systemic blood pressure in most patients with early, uncomplicated insulin-dependent diabetes (25). With enalapril treatment, a persistent 20 mmHg reduction in ΔP was observed in DM+E rats. This reduction in ΔP was accompanied by a striking reduction in ΔP to levels seen in nondiabetic control rats. This effect was accounted for by the observed reduction in mean systemic arterial pressure in the setting of persistent glomerular arteriolar vasodilatation, thus permitting this slight systemic hypotension to be shared by the glomerular capillaries. It should be stressed that values for SNGFR and Q\textsubscript{A} remained substantially elevated in enalapril-treated rats despite normalization of ΔP. The persistence of hyperfiltration can be explained by the numerically higher K\textsubscript{f} values observed in these animals (0.101±0.017 nl/(s·mmHg) vs. 0.057±0.005 in DM), thus offsetting the effect of the reduction in ΔP. Of note, in rats with 5/6 renal ablation, enalapril treatment was also associated with a similar increase in K\textsubscript{f} (11).

Diabetic rats not treated with enalapril exhibited marked
and progressive proteinuria, as well as a correspondingly high prevalence of glomerular structural abnormalities at 14 mo of diabetes. These findings indicate that long-term moderate hyperglycemia is inevitably accompanied by progressive glomerular damage in a large proportion of rats fed 24% protein chow, thus adequately reproducing the natural history of this disorder in humans. In sharp contrast with the near-exponential progression of albuminuria in untreated DM rats, enalapril treatment was associated with only slight increases in urinary albumin excretion with time, never reaching values significantly different from control. Likewise, morphological abnormalities in this group were minimal and not distinguishable from those associated with normal aging. While AP was maintained at subnormal levels in DM+E rats throughout the study, blood glucose concentration remained at nearly identical stable high levels in both diabetic groups. The proportion of glycosylated hemoglobin at the end of the study was also essentially identical in DM and DM+E rats, and well in excess of values seen in control rats. Thus, the observed differences between DM and DM+E groups regarding glomerular morphology cannot be attributed to differences in metabolic control; rather, the structural differences appear to result solely from the observed differences in glomerular hemodynamics, and in particular the differences in ΔP in the two groups. In this regard, the present findings closely resemble those previously obtained by Zatz and co-workers (7), in that only the group sustaining early glomerular hypertension eventually developed widespread glomerular injury at 14 mo of diabetes.

The precise mechanism(s) whereby intracapillary hypertension adversely affects glomerular structure has not been elucidated. Systemic arterial hypertension has long been known to increase arterial and arteriolar permeability to macromolecular tracers and to lead to structural damage of arterial walls (9, 26–28). Elevations in intracapillary hydraulic pressures are likely to exert an analogous effect. In systemic capillaries, evidence for an association between capillary basement membrane thickness and capillary pressure has been provided in a number of situations, including variation of intravascular hydrostatic pressure by gravity (29), local venous stasis (30), and long-standing congestive heart failure (31). One possible mechanism for this effect could be the stimulation of local basement membrane production by the increased capillary wall tension, in a manner analogous to the enhanced collagen synthesis observed with increased local tension in other tissues (32). At the glomerular capillary level, this tension could also lead to direct mechanical disruption of the glomerular capillary wall, giving rise to capillary microaneurysms and epithelial cell detachment from the glomerular basement membrane (28, 33). Furthermore, the increased platelet aggregability observed in diabetes (34) might further contribute to the development of diabetic glomerular injury by promoting capillary thrombosis in the presence of even minor degrees of endothelial injury. This possibility is strengthened by the observation of a protective effect of heparin against glomerular injury in the remnant kidney (35) and in nephrotoxic serum nephritis (36).

Among the etiologic factors that have been considered, recent studies have focused attention on the role played by the glomerular mesangium in the genesis of diabetic glomerulopathy. Mesangial thickening, which may be a direct or indirect consequence of an increase in the rate of deposition of circulating macromolecules, is invariably associated with segmental sclerotic lesions in diabetes (37). Other studies have suggested that increased mesangial activity is a cause of progressive glomerular injury in nephrotoxic serum nephritis and aminonucleoside nephrosis, giving rise to the so-called “mesangial overload hypothesis” (28, 38). Increased transglomerular passage of macromolecules, with consequent mesangial hyperactivity, is likely to be operative over an extended period of time in diabetic subjects before the appearance of clinical signs of diabetic nephropathy (39, 40).

Clinical studies have shown that treatment of systemic hypertension in patients with moderately advanced diabetic nephropathy retards subsequent deterioration of renal function, presumably by ameliorating abnormal glomerular capillary hemodynamics (13, 14). The present study demonstrates for the first time that long-term converting enzyme inhibition in an animal model of diabetes mellitus not only delays, but actually prevents, the establishment of diabetic glomerulopathy, largely by normalizing glomerular capillary hydraulic pressure.

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Pathophysiology of Diabetic Glomerulopathy 1929


