Influence of Antihypertensive Therapy on Development and Progression of Diabetic Glomerulopathy

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Capillary hypertension is suggested to be the underlying cause of microvascular disease affecting the kidney, the retina, and other organs and tissues in diabetic patients and animals. Hyperglycemia causes an expansion of extracellular volume, which induces a vasodilatory response. Hemodynamic adaptation to vasodilation leads to an increase in intracapillary hydraulic pressure, which subsequently causes vascular damage. In experimental animals, restoration of capillary pressure to normal levels by ingestion of a low-protein diet or administration of an angiotensin I–converting enzyme inhibitor has been shown to prevent microvascular damage in the kidney, and dietary protein restriction limits injury in the retina as well. Atrial natriuretic peptide, which is secreted by atrial myocytes in response to volume expansion, may be involved in mediation of the hemodynamic adaptation (vasodilatory response) that results in diabetic microvascular disease.
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PATHOGENESIS OF DIABETIC MICROVASCULAR DISEASE

Patients with either insulin-dependent or non-insulin-dependent diabetes whose blood glucose levels are reasonably well controlled are in a state of chronic extracellular volume expansion. This expansion results from the cotransport of greater amounts of sodium to the extracellular fluid that accompanies the increased reabsorption of glucose by the renal tubule. Among its consequences is an inexorable, sustained dilation of the microcirculation in all tissues and organs, including kidney and retina.

In the kidney, the vasodilatory response causes more of the systemic blood pressure to be transferred to the glomerular microcirculatory bed, leading to adaptive hyperfiltration and hyperperfusion and ultimately to local capillary damage. Injury to the glomerular capillaries initiates a positive-feedback loop, which results in the destruction of more and more glomeruli.

A similar cycle of events is believed to occur in the retinal circulation. Thus, the thickening of capillary basement membranes in diabetic patients may be a consequence of the capillary wall response to a prevailing hypertensive state within these vessels.

Nephropathy in the diabetic patient follows a course of inexorable progression that is slow in some patients and rapid in others. In any given patient, however, the decline in renal function appears to follow a monotonic pattern. There is almost a mathematical precision to the process, which implies a separation between the initial underlying cause of diabetic renal disease and its progression to complete loss of renal function.

Nephron loss associated with other forms of renal disease, renal ablation, and primary models of renal injury equivalent to the immunologic forms of renal disease also causes an adaptive increase in pressure and flow in the remaining glomerular population. The acquired intracapillary hypertension arising from the vasodilation induced by nephron loss is responsible for the hyperfunctioning that ultimately leads to damage and subsequent failure of yet another glomerulus, thus setting in motion a cycle of progressive destruction of the renal tissue.

In both diabetic patients and patients with systemic hypertension, a primary augmentation in glomerular pressures and flows is apparent even before any neph-

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rons are lost. Once these increases in pressure and flow are established, however, nephron loss occurs, mimicking the renal surgical reduction syndrome. Clinically, patients with the highest values for glomerular filtration rate (GFR) early in the course of diabetes are most likely to develop diabetic glomerulopathy (1).

EXPERIMENTAL FINDINGS IN DIABETIC ANIMALS

GFRs in animals with streptozocin-induced diabetes and moderate hyperglycemia greatly exceed GFRs in nondiabetic controls (2). The mechanism responsible for the hyperfiltration response in these animals is the same as that operating in animals subjected to renal ablation, i.e., a high flow rate through the glomerular capillaries and a high intracapillary hydraulic pressure. The combined actions of the increased pressure and the higher plasma flow cause a greater movement of fluid across the capillary wall, which is, in fact, the process defined by the filtration rate.

This adaptive increase in flow and pressure in the diabetic animal is a consequence of the volume expansion associated with hyperglycemia. As long as the animal remains hyperglycemic, the volume-expansion state will be maintained, resulting in renal vasodilation and overperfusion and overpressurization of the glomerulus.

Evidence from a study conducted in rats with streptozocin-induced diabetes suggests that the inevitable destruction of the glomerulus is an acquired hemodynamic maladaptation rather than a consequence of the underlying metabolic disorder (3). In this investigation, stable glucose levels were maintained throughout the 12-mo observation period by means of daily injections of long-acting insulin. Thus, on the basis of their metabolic abnormality, these animals were at a similar risk for the development of glomerulopathy. Their hemodynamic risk differed, however. The protein content of the rat chow was altered for each group, so that one group received twice the usual amount of protein, a second group was fed one-half the usual protein level, and a third group was given one-fourth the usual protein content. Because amino acids have intrinsic vasodilatory properties, a high-protein intake can be expected to cause vasodilation and, consequently, an increase in GFR.

Increasing the dietary protein content resulted in a stepwise increase in GFR in diabetic rats and in a control group of normal rats; however, the GFR exceeded normal only in the diabetic animals fed the high-protein diet. This elevation in GFR was attributed to increases in glomerular flow and glomerular pressure.

Over the 12-mo observation period, a glomerulopathy associated with very high urinary albumin excretion rates developed in the diabetic rats fed the high-protein diet. The degree of proteinuria in the diabetic rats fed reduced-protein diets was no greater than that in normal rats receiving any of the three diets.

Thus, there appears to be no intrinsic metabolic risk for glomerulopathy. The only risk that could be identified in this study was coupled with the glomerular capillary hypertension induced by the high-protein diet.

DIABETIC RETINOPATHY

Hemodynamic abnormalities characterize the extrarenal vasculature in diabetes as well (4). Ophthalmologists have described arterial and venous dilation and engorgement in the retinal circulation in the early stages of insulin-dependent diabetes. These findings can be reversed by glycemic control. Flow studies with fluorescein indicate not only dilation but also faster flow through the retinal vessels. Both of these early changes presage eventual retinopathy. Furthermore, the incidence of retinopathy is highest in diabetic patients who also have hypertension.

Additional evidence that capillary hypertension leads to microcirculatory damage comes from observations in patients with unilateral glaucoma and unilateral carotid arterial stenosis, both of which impede retinal flow on one side. In one case described in the literature, a diabetic patient had a normal retina on the same side as a carotid arterial stenosis and a grade 4 retinitis proliferans on the other side (5). Indirect ophthalmodynamometry indicated that pressures in the retinal vessels supplying the normal side were about two-thirds the systemic arterial pressure, whereas pressures in the vessels supplying the side with retinopathy were the same as the systemic arterial pressure (5). The "clamp" on the retinal circulation provided by the carotid artery stenosis appeared to have prevented a bilateral vascular risk.

In the previously mentioned diabetic rats that were fed a high-protein diet, the average retinal basement membrane thickness was clearly greater than in nondiabetic animals fed a high-protein diet or in diabetic animals fed a lower protein diet (6). Furthermore, the groups fed a high-protein diet exhibited both retinal and glomerular abnormalities.

IMPACT OF ANTIHYPERTENSIVE THERAPY

Although a reduction in dietary protein may lower capillary hypertension, low-protein diets tend to be associated with poor patient acceptance and poor compliance. Therefore, antihypertensive therapy, which is known to slow the development of clinical diabetic glomerulopathy (7), may be a more rational and effective means of reducing intracapillary pressure in diabetic patients.

The impact of antihypertensive therapy on capillary blood pressure was examined in two groups of diabetic rats given insulin to maintain a stable blood glucose level (8). One group received an angiotensin I–converting enzyme (ACE) inhibitor in their drinking water. The group that did not receive an ACE inhibitor had

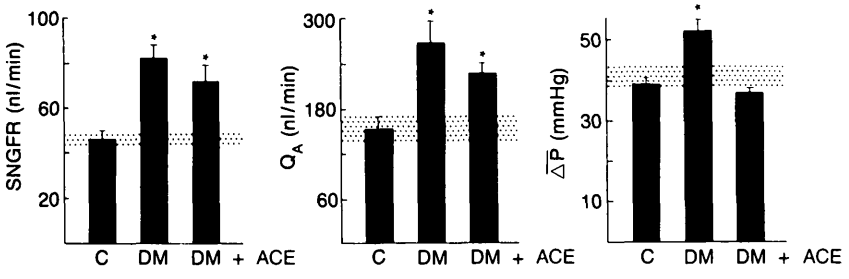

FIG. 1. Glomerular hemodynamics 4–6 wk after induction of diabetes. Decline in single-nephron glomerular filtration rate (SNGFR), plasma flow rate (Q_A), and glomerular transcapillary hydraulic pressure gradient ($\overline{\Delta P}$) in normal (C) and diabetic (DM) rats treated with angiotensin-converting enzyme (ACE) inhibitor. *Shaded areas* indicate normal range. *$P < .05$ vs. normal. [Adapted from Zatz et al. (8) with permission.]

normal but slightly higher blood pressure than did the animals that received the ACE inhibitor.

Hyperfiltration attributed to high glomerular flows and pressures was apparent in the diabetic rats that were not given the antihypertensive agent (Fig. 1). Animals that received the ACE inhibitor had a mild but insignificant reduction in GFR resulting from a slight decrease in glomerular flow and the restoration of glomerular capillary pressure to normal levels. In addition, the glomerulopathy, manifested by albuminuria, that developed in diabetic animals treated only with insulin was not observed in rats that received both insulin and the ACE inhibitor. Albumin excretion rates in the treated rats did not differ from rates associated with normal aging in the control animals.

ATRIAL NATRIURETIC PEPTIDE

Alterations in the atrial natriuretic peptide (ANP) hormone system have been suggested as a possible contributing factor to the hyperfiltration and chronic vasodilatory response in patients with diabetes. The secretion of this peptide by atrial myocytes is activated principally by volume expansion. Thus, the chronic volume expansion state associated with diabetes may result in higher circulating ANP concentrations.

Experimental data disclose remarkable similarities between diabetic rats and normal rats given a synthetic atrial peptide infusion (9). The diabetic animals had a low renal vascular resistance, which resulted in the transmission of more pressure to the glomerulus, leading to hyperfiltration. The diabetic state is also associated with low plasma levels of aldosterone and renin. Infusion of atrial peptide in normal rats results in a reduction in renal vascular resistance, a rise in glomerular pressure, and an increase in GFR along with the suppression of aldosterone and renin.

Immunoreactive ANP levels and plasma volumes in animals made diabetic by administration of streptozocin and given only enough insulin to maintain blood glucose at moderately hyperglycemic levels were higher than those in nondiabetic animals (9,10). When hyperglycemia was avoided by providing more insulin, however, volume expansion did not occur, and atrial peptide levels remained normal.

In addition, when diabetic rats were given antibodies directed against the atrial peptide, GFR reverted to normal (9). In contrast, a nonimmune serum had no effect on GFR (Fig. 2).

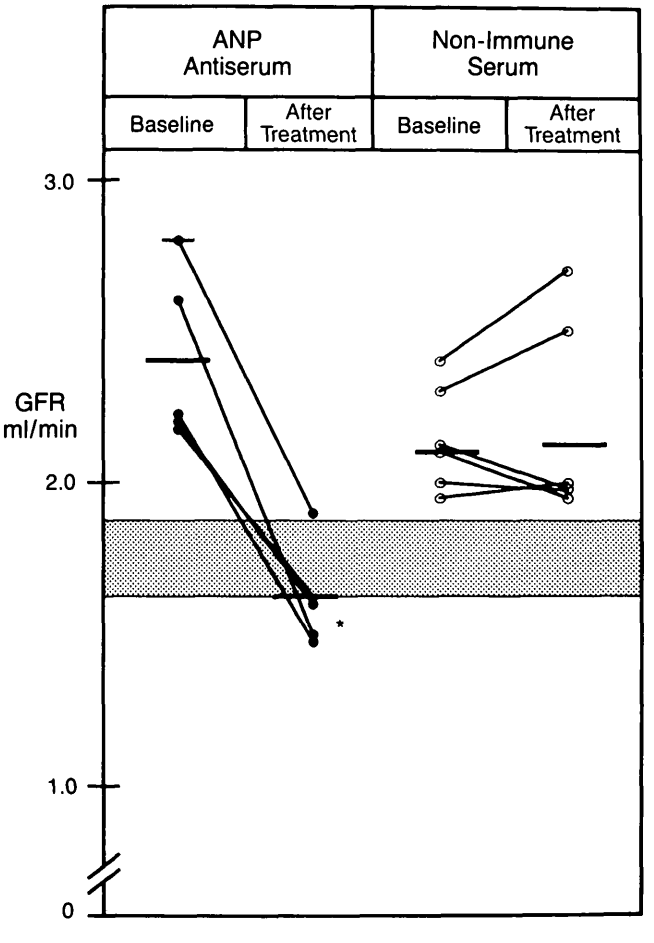

FIG. 2. Reduction in glomerular filtration rate (GFR) achieved with atrial natriuretic peptide antiserum in diabetic rats. *Shaded area* represents normal range. *$P < .001$ vs. baseline. [Adapted from Ortola et al. (9) with permission.]

SUMMARY

Evidence obtained in laboratory animals has demonstrated that the moderate level of hyperglycemia allowed by current therapeutic regimens is the underlying cause of capillary hypertension associated with diabetes mellitus. Hyperglycemia results in an expansion of extracellular volume, which induces vasodilation, the transmission of systemic pressure to the microcirculatory level, and, eventually, hypertension-mediated capillary damage. ANP may be one of the factors involved in this process. Other possible mediators are glucagon excess and reduction in renin levels.

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