Medical Staff Conference

Diabetes, Dietary Protein and Glomerular Hyperfiltration

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Despite the availability of insulin for the prevention and treatment of the metabolic abnormalities in diabetes mellitus, microvascular complications involving the eye, kidney and nervous system develop in many patients with this disorder. Diabetic nephropathy, in particular, represents one of the major causes of morbidity and mortality facing patients with this disease. Drs Burl Don and Morris Schambelan will discuss the current understanding of the pathogenesis of diabetic nephropathy and other forms of chronic renal disease and potential therapeutic approaches that may retard or prevent their progression.*

BURL R. DON, MD,† and MORRIS SCHAMBELAN, MD‡: Recently a series of provocative clinical and experimental observations has identified several pathophysiologic states in which the glomerular filtration rate (GFR) is supernormal. This phenomenon (called "glomerular hyperfiltration") and an associated increase in the glomerular transcapillary hydraulic pressure difference ("glomerular hypertension") occur in disorders such as diabetes mellitus[1-5] and in remnant nephrons following subtotal nephrectomy[6] and are modified by alterations in certain dietary constituents, particularly protein.[7,8] Although this increase in GFR has sometimes been thought to be a useful adaptation, particularly after the loss of functioning renal mass, there is a growing body of evidence suggesting that such altered glomerular hemodynamics may be deleterious to renal function by initiating a pathogenetic sequence that eventuates in anatomic damage and proteinuria (Figure 1).[9-11]

The mechanisms by which the increases in GFR and proteinuria occur are largely unknown. We will review the evidence that suggests that abnormalities of glomerular eicosanoid production occur and play a pathophysiologic role in states associated with glomerular hyperfiltration and hypertension. Particular emphasis will be given to studies done in patients and experimental animals with diabetes mellitus, inasmuch as this is the prototypic disorder that is characterized by these glomerular hemodynamic abnormalities. In addition, we will also review data that suggest that glomerular eicosanoids may play a role in the glomerular hemodynamic changes that occur following a reduction in functioning renal mass and in response to an alteration in dietary protein intake. Finally, we will consider the role of the renin-angiotensin system and of the interaction between angiotensin II and glomerular eicosanoids in the pathogenesis of glomerular hyperfiltration.

Abnormalities of Glomerular Function in Diabetes Mellitus

Abnormalities of glomerular function are prominent features of diabetes mellitus. In approximately 40% of patients with type I (insulin-dependent) diabetes and in a somewhat smaller percentage of persons with type II (non-insulin-dependent) diabetes, diabetic nephropathy will develop, characterized by proteinuria, a loss of renal function and a rapid progression to end-stage renal failure.[12] The clinical features and pathogenesis of this important cause of chronic renal insufficiency were reviewed recently in this forum[13] and elsewhere.[14]

Before the onset of overt clinical diabetic nephropathy and progressive renal insufficiency, many persons with diabetes, particularly those with type I diabetes who were studied early in the course of their disease, have had a supernormal GFR and renal plasma flow (Figure 2).[15,16] Retrospective analysis of the subsequent course in such patients suggests that such hemodynamic abnormalities, together with the presence of microalbuminuria and systemic hypertension, may herald the subsequent development of diabetic nephropathy.[17]

That some component of the metabolic derangement in diabetes is responsible for the alterations in glomerular hemodynamics is evidenced by the observation that "tight control" with insulin will prevent or correct the hyperfiltration in both patients with clinical diabetes mellitus[18-20] and in animals in which diabetes is induced experimentally with streptozocin (streptozotocin).[21] Structural hypertrophy, typically seen in kidneys of diabetic patients and animals,[22] may account in part for these findings. Indeed, the increased GFR and renal plasma flow correlate with renal size in patients with type I diabetes.[15,23] In diabetic rats a pronounced increase in renal weight and cellular hypertrophy can be detected within the first 24 hours after the onset of hyperglycemia.[22]

Hyperglycemia per se may play a role as evidenced by the increase in GFR that occurs with infusion of glucose in both normal subjects and in persons with insulin-dependent diabetes[24] and by the reduction in the elevated levels of GFR and renal plasma flow in type I diabetes that results when glucose levels are normalized by short-term, intense insulin therapy.[25]

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
ANP = atrial natriuretic peptide
GFR = glomerular filtration rate
HPLC = high-performance liquid chromatography
PG = prostaglandin
TX = thromboxane
UCSF = University of California, San Francisco

In addition to hyperglycemia, the diabetic state is characterized by increased circulating levels of glucoregulatory hormones such as glucagon and growth hormone, both of which can induce an increase in the GFR.[26-28]

The pathogenesis and pathophysiologic significance of glomerular hyperfiltration in diabetic nephropathy have been elucidated further in studies done in rats with experimentally induced diabetes mellitus. Similar to the findings in humans with type I diabetes, the whole-kidney GFR is increased 30% to 40% above control in rats made diabetic with the β-cell toxin streptozocin.[4] The determinants of GFR in this model have been assessed using the technique of free-flow micropuncture. Such studies in Munich-Wistar rats have identified the major physical determinants of the GFR: glomerular plasma flow, afferent protein concentration, transcapillary hydraulic-pressure difference and the glomerular capillary ultrafiltration coefficient.[29] These micropuncture studies indicate that, in diabetic rats, the single-nephron GFR and glomerular capillary plasma flow are increased as a consequence of renal vasodilatation.[4] In addition, the transglomerular capillary pressure difference is increased.[4] Such glomerular hypertension appears to play a critical role in the initiation and progression of diabetic nephropathy. This concept stems from the observation that, before inducing diabetes mellitus in rats, a unilateral reduction in renal perfusion pressure due to placing a clip across one renal artery attenuated the subsequent development of diabetic nephropathy in the "clipped" kidney.[30] Similarly, the occurrence of a unilateral atherosclerotic plaque in a renal artery of a diabetic patient[31] protected the ipsilateral kidney from diabetic nephropathy, whereas the contralateral kidney with a patent renal artery showed Kimmelstiel-Wilson lesions. Furthermore, despite persistent hyperglycemia, glomerular damage and proteinuria in rats can be prevented by maintaining intraglomerular pressures at normal levels using either dietary[8] or pharmacologic means[32] (discussed later). Thus, the degree of intraglomerular hypertension appears to be more important than the metabolic derangement in the pathogenesis of diabetic nephropathy.

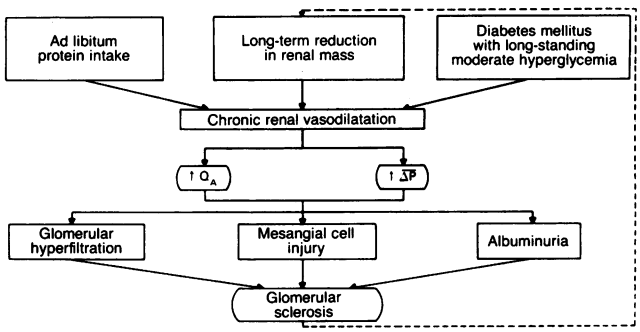

Figure 1.—Summary of the hypothesis of Brenner and associates that indicates a role for sustained increases in glomerular pressures and flows in the initiation and progression of glomerular damage. In this model it is proposed that ad libitum protein intake, reduction in renal mass and diabetes mellitus all lead to renal vasodilatation as reflected by an increase in glomerular capillary plasma flow rate (Q_A), and an increase in glomerular transcapillary hydraulic pressure (ΔP). The resulting loss of functioning nephrons sets up a vicious cycle (dashed line) whereby the reduction in renal mass leads to further hyperfiltration and eventual destruction of the remaining functioning nephrons. (Reprinted with permission from Brenner.[11])

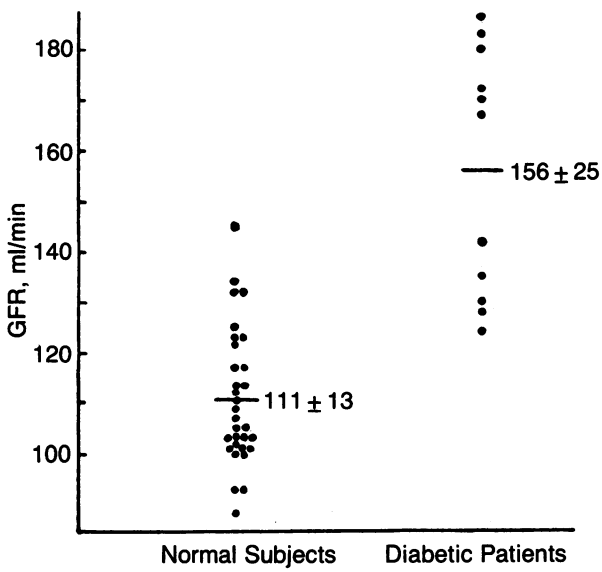

Figure 2.—Comparisons of measurements of the glomerular filtration rate (GFR) in 11 patients with untreated type I diabetes mellitus and 31 normal subjects. The difference between groups was significant ($P < .001$). (Reprinted with permission from Mogensen.[2])

Abnormalities of Glomerular Eicosanoid Metabolism in Diabetes Mellitus

It has been suggested that abnormalities of vasoregulatory hormones may play a role in the pathogenesis of glomerular hyperfiltration.[8] Several classic circulating hormones, such as parathyroid hormone and vasopressin, and other biologic messengers that are produced in the kidney and that act locally through an autocrine or a paracrine mechanism—eicosanoids, angiotensin II—can affect the GFR.[33] In addition to vasoactive effects on the afferent and efferent renal arterioles with subsequent alteration of renal vascular resistance, many of these substances affect the filtration process by a reduction in the glomerular capillary ultrafiltration coefficient, an action that appears to be mediated by contraction of the glomerular mesangial cell and reduction of the glomerular capillary surface area. This may be due to a direct contractile effect of the agonist on the mesangial cell, as in the case of angiotensin II and vasopressin, or by secondary activation of the renin-angiotensin system.[33,34] Prostaglandins, which are secreted by whole glomeruli[35-37] and by cultured glomerular mesangial cells,[38-40] can influence the GFR by modifying the vasoconstrictor effects of angiotensin II[41] and the glomerular contractile response to this agonist.[42]

To evaluate directly the effect of diabetes mellitus on glomerular eicosanoid metabolism, we did studies in the early stages of an experimental model of diabetes mellitus in rats.[43] Control rats, which were matched for age and weight at the time of intravenous administration of streptozocin, received an equal volume of the vehicle. The onset of diabetes was manifested by the development of polyuria and polydipsia within two to three days of administering streptozocin. Substantial hyperglycemia occurred promptly in the rats that re-

ceived streptozocin and tended to increase further during the subsequent weeks of observation.

Studies of eicosanoid metabolism were done 9 to 23 days after administering streptozocin. Glomeruli were isolated by mechanical sieving. Eicosanoid production was evaluated both by direct radioimmunoassay and by identification of labeled products by high-performance liquid chromatography (HPLC) after incubation with arachidonic acid labeled with carbon 14. Glomerular prostaglandin (PG) production was increased in diabetic rats. In studies done in individual rats, the mean production rates of both PGE_2 and $PGF_{2\alpha}$, the major prostaglandins produced by rat glomeruli, were approximately twofold greater in the rats with diabetes, whereas those of thromboxane (TX) B_2 were not significantly greater than of controls (Figure 3). PGE_2 production was also measured on the supernatant obtained from incubating pools of glomeruli from diabetic and control rats. In these studies, the mean basal PGE_2 production was also about twofold greater in glomeruli from diabetic animals. When metabolism of arachidonic acid ^{14}C was evaluated by HPLC, conversion to labeled PGE_2, $PGF_{2\alpha}$ and TXB_2 and hydroxyheptadecatrienoic acid by diabetic glomeruli was twofold to threefold greater compared with that in control glomeruli, whereas no significant difference in conversion to 12- and 15-hydroxyeicosatetraenoic acid occurred. These findings indicate that glomerular cyclooxygenase but not lipoxygenase activity was increased in the diabetic animals.

The increased rate of prostaglandin production did not appear to be due to a nonspecific effect of streptozocin inasmuch as glomerular prostaglandin production was not increased significantly in streptozocin-treated rats made euglycemic with insulin therapy. The increased rate of prostaglandin production also did not appear to be related directly to the severity of the diabetic state as reflected by the degree of hyperglycemia at the time of death. In fact, the rates of glomerular prostaglandin production in the individual diabetic animals correlated inversely with the plasma glucose concentration.

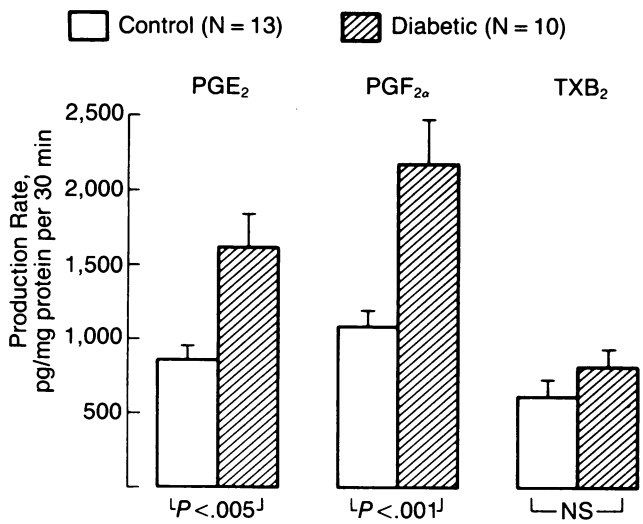

Figure 3.—Comparison of eicosanoid production by glomeruli isolated from rats with streptozocin-induced diabetes mellitus and control animals. Production rates were assessed by direct radioimmunoassay of the supernatant after incubating the glomeruli for 30 min at 37°C. Production rates for both prostaglandin (PG) E_2 and $PGF_{2\alpha}$ were twofold greater in the diabetic animals, whereas the production of thromboxane (TX) B_2 was not significantly (NS) greater than in controls. (Adapted from data in Table 1 in Schambelan et al.[43])

Similar increases in glomerular prostaglandin synthesis in diabetic rats have now been reported by other investigators.[44,45] Taken together with the results of our study, it appears that, at least in the early stages of the disorder, glomerular prostaglandin synthesis is increased in glomeruli from diabetic rats.

The functional significance of this augmented production of glomerular prostaglandins observed in diabetic animals is suggested by studies using cyclooxygenase inhibitors as pharmacologic probes of the renal circulation. Treatment with cyclooxygenase inhibitors—indomethacin, acetylsalicylate—prevented glomerular hyperfiltration when administered in the early stages of experimental diabetic nephropathy in rats,[45,46] reduced intraglomerular hypertension[47] and prevented the progressive decrease in the GFR characteristic of the chronic stages of this model.[46] Although studies evaluating the effect of long-term treatment with cyclooxygenase inhibitors in humans with glomerular hyperfiltration have not been reported, short-term infusion of lysine acetylsalicylate significantly reduced the supernormal GFR and renal plasma flow in patients with type I diabetes mellitus.[48]

Abnormalities of Glomerular Function Following a Reduction in Renal Mass

As renal mass is reduced, the remaining nephrons increase in size and function. Studies in dogs[49] and in rats[50] have shown that glomerular hyperfiltration occurs following partial renal ablation, and the degree of this functional adaptation correlates with the amount of renal mass removed. Deen and co-workers[6] found that the single-nephron GFR was increased in remnant nephrons from rats with partial renal ablation. Similar to the glomerular hemodynamic profile that occurs in rats with streptozocin-induced diabetes mellitus, the determinants of this elevated single-nephron GFR were noted to be an increase in the glomerular transcapillary hydraulic pressure gradient and glomerular plasma flow rate, occurring as a consequence of glomerular arteriolar vasodilatation. Such altered glomerular hemodynamics result in progressive azotemia, proteinuria and glomerulosclerosis. In 1932 Chanutin and Ferris[51] reported that proteinuria, hypertension and progressive dysfunction occurred in rats subjected to three-quarters renal ablation. Studies by Shimamura and Morrison[52] and by Olson and associates[53] have documented that progressive histologic changes occur in remnant nephrons following subtotal nephrectomy, which include fusion of epithelial foot processes, expansion of the mesangium, collapse of the capillary lumen and subsequent focal and segmental glomerular sclerosis. Ultrastructural changes have been shown as early as one week after partial renal ablation.[53] Thus, functioning remnant nephrons, which augment their filtration and plasma flow as an apparent compensatory measure, undergo an acceleration of their own destruction following renal injury.

Effect of Partial Renal Ablation on Glomerular Eicosanoid Metabolism

The concept that vasodilatory prostaglandins may mediate an elevated single-nephron GFR and glomerular capillary plasma flow rate in functioning remnant nephrons is not surprising inasmuch as inhibition of renal prostaglandin synthesis in several experimental and clinical renal diseases results in a reduced renal blood flow and GFR.[54] We and other investigators have shown that glomerular production of

PGE_2, the major vasodilatory eicosanoid produced by the rat glomerulus, is greater in rats with partial renal ablation as compared with controls having a sham operation.[55] Inhibition of cyclooxygenase activity with indomethacin significantly reduced the GFR in rats with partial renal ablation, but not in control rats.[55] Similarly, recent micropuncture studies have shown that reducing renal prostaglandin production with indomethacin attenuated the augmented single-nephron GFR in rats with subtotal nephrectomies, whereas this therapy had no effect on the glomerular microcirculation in sham-operated controls.[56] These studies at both the whole-kidney and single-nephron level suggest that renal prostaglandin production plays an important role in the augmented renal hemodynamic response to partial renal ablation. Thus, like diabetes mellitus, rats with partial renal ablation may share a common dependency on renal eicosanoid biosynthesis in mediating glomerular hyperfiltration.

Role of Dietary Protein Intake in the Progression of Renal Disease

An increasing body of evidence supports an important role for dietary protein intake in the pathogenesis of glomerular hyperfiltration and the progression of renal insufficiency.[57] Several investigators in the 1920s to 1940s noted the deleterious effect of a high-protein intake in accelerating the progression of renal disease and recommended a reduction in protein intake in patients with chronic renal disease for the purpose of reducing the "workload" of the functioning nephrons.[58] Although restriction of dietary protein intake had long been recognized to reduce the symptoms of uremia and thus to play an important role in the conservative management of this disorder, with the advent of dialysis in the 1950s and 1960s, less attention was paid to the possible role of dietary therapy in retarding the progression of renal disease. Hostetter and colleagues[7] more recently showed an important link between dietary protein intake, altered glomerular hemodynamics and subsequent renal damage. Following partial renal ablation, glomerular hyperfiltration and hypertension failed to develop in rats fed a low-protein (6%) diet, whereas animals fed standard rat chow (containing 24% protein) showed typical elevations in single-nephron GFRs and glomerular hydraulic pressure (Figure 4). Additionally, prevention of glomerular hyperfiltration and hypertension by restricting protein intake was associated with preservation of normal glomerular histology. This important effect of dietary protein on glomerular hemodynamics has also been observed in normal rats: Ichikawa and co-workers[59] noted a decrease in the glomerular capillary plasma flow in rats fed a low-protein diet. Further, short- and long-term protein loads increase the GFR and renal plasma flow in both normal human subjects[60,61] and in experimental animals.[62,63] The clinical relevance of these observations has been supported by several studies that have evaluated the role of dietary protein restriction on the progression of renal disease in humans. For example, Maschio and associates[64] have shown that restricting the dietary protein intake in patients with early renal insufficiency greatly slowed the rate of deterioration of their renal function (Figure 5). Similar salutary effects on renal function have been achieved by Mitch[65] using low-protein diets supplemented with essential α-ketoanalogues.

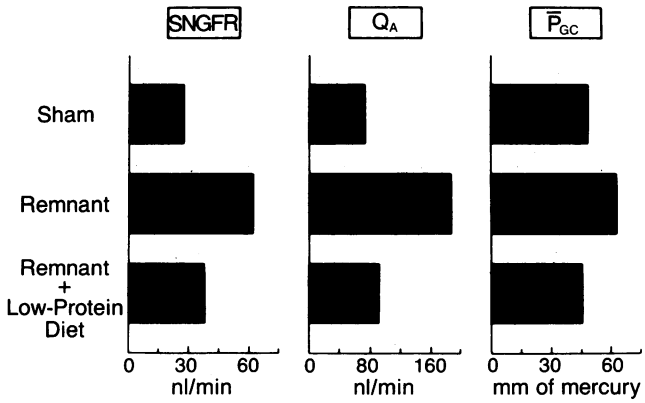

Figure 4.—Single-nephron glomerular filtration rate (SNGFR), glomerular capillary plasma flow rates (Q_A) and glomerular capillary hydraulic pressures ($\bar{P}_{GC}$) in rats with remnant nephrons following subtotal nephrectomy and sham-operated controls. Subtotal nephrectomy results in an augmentation in SNGFR, Q_A and $\bar{P}_{GC}$ in rats having a standard (24%) protein intake. Reducing dietary protein intake from 24% to 6% blunted these renal hemodynamic increases in the rats with remnant nephrons to levels observed in the sham-operated controls. Further, dietary protein restriction was associated with a preservation of normal glomerular histology and a decrease in proteinuria in the animals with subtotal nephrectomies. (Adapted from data in Table 1 with permission from Hostetter et al.[7])

Effect on Glomerular Eicosanoids of Varying Dietary Protein Intake

We have undertaken studies to determine the effect of varying the dietary protein intake on glomerular eicosanoid production in rats with Heymann nephritis. This is an immunologically mediated renal disease with many similarities to human membranous glomerulopathy. Heymann nephritis was induced by the intraperitoneal injection of FX1A antiserum.[66] Two days following induction of the model, an equal number of rats from each paradigm was randomly selected to receive either a high (40% casein)- or low (8.5% casein)-protein diet. The two diets were rendered isocaloric by adjusting the sucrose and dextrin contents. Dietary protein intake modulated glomerular prostaglandin production in these animals. Production rates of PGE_2, $PGF_{2\alpha}$ and TXB_2 were all significantly greater in glomeruli isolated from the rats with Heymann nephritis fed the high-protein diet in comparison to rats fed the low-protein diet. The degree of albuminuria was also greater in the rats ingesting the high-protein diet. A similar modulation of glomerular eicosanoid production by dietary protein intake has also been shown to occur in preliminary

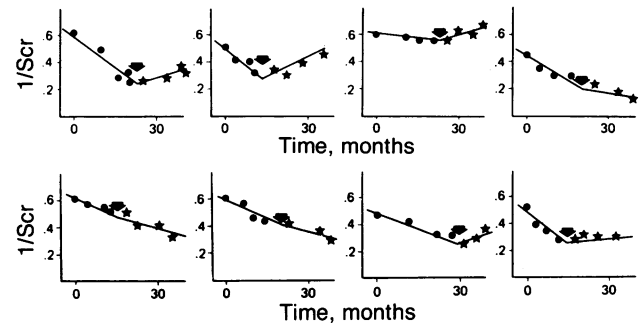

Figure 5.—Plot of the reciprocal of serum creatinine concentration as a function of time in 8 patients with chronic renal insufficiency before **(closed circles)** and after **(stars)** instituting dietary protein restriction **(arrows)**. The difference between the mean values of the slopes before (−0.0132) and after (−0.0013) protein restriction was significant ($F = 6.57$, $P < .01$). Thus, the rate of deterioration of renal function was attenuated by dietary protein restriction. (Reprinted with permission from Maschio et al.[64])

studies done in diabetic rats, rats with partial renal ablation and in normal animals.[67]

Several lines of evidence implicate renal eicosanoids in the increases in GFR and renal plasma flow that occur with protein intake in both humans and experimental animals. Renal production of eicosanoids is augmented following protein loading as reflected in the increased urinary excretion of PGE_2 with amino acid infusions in normal humans[68] and the elevated urinary PGE_2 and 6-keto-$PGF_{1\alpha}$ excretion following the ingestion of a high-protein diet in patients with chronic glomerular diseases.[69] The increase in GFR and renal plasma flow that occurs in response to infusions of arginine[70] or amino acid mixtures[68] or ingesting a meat meal[71] in normal human subjects can be blunted by pretreatment with cyclooxygenase inhibitors. Similar observations have been noted in rats with experimental renal disease and in normal animals. For example, urinary excretion of 6-keto-$PGF_{1\alpha}$ and PGE_2 was increased in normal rats on a long-term high-protein diet.[72] Further, pretreatment with indomethacin blocked both the increase in GFR and glomerular production of PGE_2 and 6-keto-$PGF_{1\alpha}$ that occurred in response to a short-term protein load.[73] Indomethacin treatment also prevented both the short-term increase in the GFR following a protein bolus in uremic rats[73] and the parallel increases in GFR and urinary excretion and glomerular production of 6-keto-$PGF_{1\alpha}$ associated with long-term ingestion of a high-protein diet in rats with Adriamycin (doxorubicin hydrochloride) nephrosis.[74]

The Renin-Angiotensin System and Glomerular Hypertension

The renin-angiotensin system has been implicated in the alteration in glomerular function that occurs in animals with various renal diseases. Anderson and colleagues[75] found that the angiotensin-converting enzyme (ACE) inhibitor, enalapril, was not only effective in treating the systemic hypertension following partial renal ablation in rats but, in addition, lowered the glomerular transcapillary hydraulic pressure. Furthermore, treatment with enalapril significantly limited the development of proteinuria and glomerular lesions. These investigators subsequently showed a therapeutic advantage of ACE inhibitors in retarding the progression of renal disease as compared with a standard antihypertensive regimen—reserpine, hydralazine hydrochloride and hydrochlorothiazide.[76] Whereas both enalapril and the standard antihypertensive therapy were effective in lowering systemic blood pressures in rats with partial renal ablation, only enalapril was effective in lowering the glomerular transcapillary hydraulic pressure and in limiting progressive proteinuria and glomerular damage.[76] Thus, control of the systemic blood pressure was inadequate in preventing progressive renal damage unless glomerular capillary pressure was also reduced. A similar beneficial effect of ACE inhibitor therapy in reducing the glomerular capillary pressure and preventing renal damage occurs in diabetic rats.[32] Treatment with angiotensin-converting enzyme inhibitors also reduced established proteinuria in rats with Heymann nephritis[77] and in patients with diabetes mellitus.[78] In addition, there has been a recent observation that ACE inhibitor therapy reduces the rate of deterioration of the GFR in patients with diabetic nephropathy.[79]

The advantage of therapy with an ACE inhibitor is probably related to its unique effect to decrease efferent arteriolar resistance,[75] possibly by reversing the preferential effect of angiotensin II on efferent arterioles.[80] This results in a reduction of glomerular capillary hydraulic pressures. Despite the "normalization" of glomerular pressures and protection against renal damage, therapy with enalapril did not lower the single-nephron GFR or glomerular plasma flow rate in rats with partial renal ablation and diabetes mellitus. Thus, it appears that glomerular hypertension rather than hyperfiltration is the factor responsible for glomerular injury.

The quantity of protein in the diet may also be a determinant of the activity of the renin-angiotensin system, as reflected by the levels of renin in the systemic circulation. In normal rats ingesting a high-protein diet, plasma renin activity was about threefold greater than in animals fed a low-protein diet.[72] Similar results have been observed in patients with chronic glomerular diseases. In such patients, the plasma renin activity was twofold greater while they ingested a high-protein diet than when they were maintained on a low-protein diet[69] and increased abruptly following the ingestion of a large protein meal.[81] That the renin-angiotensin system plays a role in modulating glomerular function by dietary protein is suggested by the observation that the salutary effect of a low-protein diet in reducing both glomerular capillary pressures and renal injury in experimental renal disease can be duplicated by ACE inhibitor therapy.[32,75] This is in accord with our recent observation that treatment with enalapril completely prevented the increment in urinary albumin excretion that occurred as a result of consumption of a high-protein diet in rats with Heymann nephritis.[77] Because dietary protein restriction or ACE inhibitor therapy can induce a similar glomerular hemodynamic effect, Paller and Hostetter[72] have suggested that reduced dietary protein alters renal hemodynamics by lowering intrarenal renin generation and angiotensin II levels.

Interrelationship of Renal Autacoids in Regulating Glomerular Hemodynamics

Inasmuch as renal hyperfiltration results from reduced arteriolar vascular resistance and an increased renal plasma flow, it would be difficult to ascribe the hemodynamic profile in states of glomerular hyperfiltration solely to a primary alteration in the glomerular action of angiotensin II. For example, infusing angiotensin II in rats results in an increase in renal vascular resistance and a decrease in the glomerular capillary ultrafiltration coefficient, with a resultant decrease in the glomerular capillary plasma flow rate and the single-nephron GFR.[82] Because hyperfiltration is associated with an increase in glomerular capillary plasma flow rate and the single-nephron GFR, a renal vasodilator must be present. Based on the studies presented, we suggest that the glomerular vasodilatation and hyperfiltration induced by diabetes mellitus, dietary protein intake and a reduced renal mass are mediated in part by an augmented glomerular production of vasodilatory prostaglandins. Other renal vasodilators may participate in this phenomenon, including atrial natriuretic peptide (ANP). In a preliminary study by Ortola and coworkers,[83] both GFR and ANP levels were elevated in rats with moderate hyperglycemia. Further, infusing a specific ANP antiserum reversed the renal hyperfiltration. Angiotensin may contribute to this hemodynamic effect by increasing the postglomerular arteriolar tone so that, while the total renal vascular resistance is decreased, a relatively greater vasodilatation in the afferent renal arteriole could account for the increased intraglomerular pressure that is characteristic in this setting. Thus, there is probably a critical

interplay between renal eicosanoids, the renin-angiotensin system and perhaps other humoral mediators in modulating glomerular hyperfiltration and hypertension. This interaction can be predicted to be complex because, on the one hand, angiotensin II stimulates prostaglandin production by whole glomeruli[37,38] and cultured mesangial cells and, on the other, renin secretion and the subsequent angiotensin II production are in part mediated by prostaglandins.[84,85]

In summary, glomerular hypertension and hyperfiltration appear to be the major pathogenic factors in the progression of renal insufficiency in several models of experimental renal disease and are modified by the quantity of protein in the diet. The altered renal hemodynamics that occur in humans with diabetes mellitus, in experimental models of renal disease in rats and in response to protein loading have a common dependency on both renal eicosanoid biosynthesis and the renin-angiotensin system. These and other autacoid systems may be a final common pathway through which these hemodynamic changes are mediated. Thus, perturbations of these vasoactive glomerular autacoids may be responsible for both renal disease and dietary protein-induced hemodynamic abnormalities that lead to progressive renal dysfunction in clinical and experimental kidney diseases.

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