Effect of Angiotensin-Converting Enzyme Inhibition on Renal Function and Albuminuria in Normotensive Type I Diabetic Patients

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Normotensive patients with insulin-dependent (type I) diabetes mellitus (n = 18) were given 25 mg captopril (b.i.d.) and placebo for 3 mo in a randomized double-blind crossover study. Patients had normal renal function, and none had retinopathy. Albuminuria was <20 μg/min in 12 patients and between 20 and 200 μg/min in the other 6. Patients were examined at the end of the placebo and captopril phases. Captopril caused little reduction in blood pressure obtained by 24-h ambulatory monitoring (systolic 126.0 ± 2.7 to 123.9 ± 2.4 mmHg, $P < 0.08$; diastolic 74.2 ± 1.9 to 72.1 ± 1.9 mmHg, $P < 0.09$). Captopril lowered glomerular filtration rate from 99.5 ± 7.7 to 71.0 ± 5.5 ml · min^{-1} · 1.73 m^{-2} ($P < 0.01$), whereas renal plasma flow (443.9 ± 15.2 ml · min^{-1} · 1.73 m^{-2}) remained unchanged. Filtration fraction was reduced from 22.4 ± 1.4 to 17.4 ± 1.4% ($P < 0.01$). Urinary albumin excretion was reduced from 59.1 ± 0.15 to 27.7 ± 13.9 μg/min ($P < 0.1$). Reduction was related to the extent of initial albuminuria ($r = 0.997$, $P < 0.001$), a relationship that remained significant after logarithmic transformation ($r = 0.540$, $P < 0.02$). Dextran clearance was used to determine glomerular capillary function. Angiotensin inhibition caused reduction in effective glomerular pore size and also reduced flow via the nondiscriminatory shunt. Angiotensin inhibition in normotensive patients with type I diabetes was well tolerated. Reduction in albuminuria is mediated by a combination of hemodynamic changes and alterations in glomerular capillary function. *Diabetes* 41:62–67, 1992

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Nephropathy in subjects with insulin-dependent (type I) diabetes mellitus is a major complication that leads to renal failure and death. The relentless progression to end-stage renal disease is signaled by the appearance of persistent proteinuria. The presence of increased low-level albumin excretion (microalbuminuria) has been used to define an earlier phase of incipient diabetic nephropathy. Alterations of intrarenal hemodynamics causing intraglomerular capillary hypertension have been proposed as a factor in this phase of diabetic nephropathy. Moreover, increased blood pressure is an important feature of diabetic nephropathy. Aggressive treatment of hypertension slows the rate of progression toward end-stage renal failure. In this setting, angiotensin-converting enzyme (ACE) inhibitors should be beneficial, because they reduce efferent arteriolar resistance and hence diminish intraglomerular pressure. Various studies have examined the effect of ACE inhibitors in diabetic nephropathy and have demonstrated reduction in albuminuria in patients with and without hypertension.

Hemodynamic alterations as a cause of nephropathy would argue for a treatment intervention at the earliest possible time. We performed a double-blind, placebo-controlled, crossover study of the effect of the ACE inhibitor captopril in normotensive patients with type I diabetes mellitus. The effect of ACE inhibition on albumin excretion rate (AER) and glomerular capillary function has not been studied in this population. The study demonstrated significant effects of ACE inhibition on renal function, albumin excretion, and glomerular permeability without effect on random blood pressure.

RESEARCH DESIGN AND METHODS

The patients were recruited from the outpatient population of the University of Kansas Medical Center (n = 18).

TABLE 1
Clinical characteristics of insulin-dependent diabetic patients

Age (yr)	25.9 ± 2.3
Weight (kg)	79.14 ± 2.96
Height (cm)	179.2 ± 2.0
Body surface area (m^2)	1.97 ± 0.04
Diabetes (yr)	11.25 ± 1.59
Insulin (U/day)	61.80 ± 7.59

Values are means ± SE for 18 patients.

All patients gave informed consent. The clinical characteristics are given in Table 1. All patients had a diagnosis of type I diabetes mellitus confirmed by history and laboratory findings. Participants had normal renal function (creatinine <106.1 μM) and blood pressure (<140/90 mmHg) by repeated Doppler measurements (Dinamap 1846 SX) during office visits before the study, and none took antihypertensive medication. The patients did not have any evidence of retinopathy (fundus photography) or neuropathy (clinical exam).

Patients were randomly assigned to take either placebo or an ACE inhibitor for periods of 12 wk and were crossed over for an additional 12 wk. Allocation of patients to active drug (25 mg captopril b.i.d.) or placebo was done in double-blinded fashion through the pharmacy of the University Hospital. Patients with an AER <20 μg/min (n = 12) were randomized separately from those with AER >20 μg/min (n = 6) to ensure an even distribution of subjects with high and low AER. Drug and placebo were provided courtesy of Squibb (Princeton, NJ). Renal function tests and AER were determined at the beginning, at crossover, and at the end of the study.

Blood pressure measurements were taken from the 24-h average of ambulatory blood pressure recordings (SpaceLabs 90202). These recordings were done at 20-min intervals in the 24 h preceding the renal function test. Casual blood pressure was determined as the average of three sphygmomanometer readings taken on the morning of the renal function test. Other laboratory values were determined on the morning of the renal function test. Creatinine and fasting glucose concentrations in plasma or urine were determined by a standard autoanalyzer technique (Technicon). Participants received written and verbal instructions on the timed collection of urine. Urinary albumin excretion was determined by timed collections of urine in standard plastic containers without additive. Collections began after an initial morning void, which was discarded, and the time was recorded on prepared forms. Separate day and night collections were combined to yield a 24-h timed urine collection. The volume of a collection was measured with graduated cylinders, and aliquots were frozen at −20°C until analyzed.

Albumin concentration was measured in thawed urine specimens with a double-antibody radioimmunoassay (Diagnostic, Los Angeles, CA). The approximate sensitivity of the assay is 1 μg/ml with intra- and interassay coefficients of variation of ~3% for a concentration range of 5–30 μg/ml. Specimens with concentrations >30 μg/ml were diluted to determine albumin concentration within the preferred range. AER was expressed as micrograms per minute and corrected for a body surface area of 1.73 m^2.

Renal function testing included measurements of glomerular filtration rate (GFR) and renal plasma flow (RPF) during water-induced diuresis as described previously (1). In brief, the patients were tested in the fasting state; half of the regular insulin dosage was given on the morning of the study. Blood glucose concentration was maintained between 5.6 and 13.4 mM by intake of fluids containing sucrose. Diuresis was initiated with an oral load of water (1% of body wt, limit 1 L) given over 20 min and maintained with 150 ml water orally every 30 min. Except for urination, patients remained in a comfortable sitting position for the rest of the study.

Initial baseline urine and plasma samples were obtained. Patients received a priming dose of isotopes followed by a constant isotope infusion. The clearance of [^{99}Tc]technetium represented glomerular filtration rate, whereas that of [^{131}I]iodohippurate (Squibb) represented RPF. Urine and plasma samples were collected every 30 min in the subsequent nine sample periods. The average of clearance periods 6–9 was used to calculate GFR and RPF for further comparisons. Specific activity of [^{99}Tc] technetium and [^{131}I]iodohippurate in urine and plasma were determined in a Hewlett Packard dual-channel γ-scintillation spectrometer. Excretion of x was determined from urinary concentration (U_x) and volume (V), whereas clearance was determined by the standard formula $U_x \times V/P_x \times t$, where P represents plasma concentration, and t is time in minutes. All results were corrected for 1.73 m^2 body surface.

Clearance of dextran was used to determine glomerular permeability. Polydisperse dextran was given as a mixture of 40 ml each dextran 40 and dextran 70 (Macrodex and Rheomacrodex, Pharmacia, Piscataway, NJ) together with the priming dose of the other clearance markers. Sampling period 7 was used as the urine specimen, whereas adjacent plasma samples were used to provide a mixed plasma sample. Size-dependent fractionation was done with high-pressure liquid chromatography, and size-dependent concentrations were determined by a refractometer (Shimadzu RID-6A, Kyoto, Japan). The column consisted of a guard column in series with TSK 3000SW and TSK 2000SW (Varian, Walnut Creek, CA). It was standardized with reagent grade dextran (Sigma, St. Louis, MO) of M_r 9400, 39,000, 72,200, and 480,000. Molecular diameters were calculated from elution volumes, and void volume was determined with dextran blue (2,3). Eluent was distilled water with 0.15% NaN_3 at a flow rate of 1 ml/min. Samples of plasma and urine were deproteinized with trichloroacetic acid. Excess acid and small molecular impurities were removed by dialysis in collodion bags with a molecular cutoff of 3000 M_r. Each sample was analyzed in the presence of an internal dextran blue standard. Refractometer sampling was done continuously (recorded at a rate of s^{-1}). In the range between 20 to 60 Å, this resulted in about six to eight measurements obtained for each discrete increase of 1 Å. The measurements were used to calculate a geometric mean urine/plasma dextran frac-

TABLE 2
Effect of 25 mg b.i.d. captopril on basic laboratory tests

	Placebo	Captopril
Sodium (mM)	137.7 ± 2.7	136.8 ± 2.7
Potassium (mM)	4.4 ± 0.1	4.5 ± 0.1
Creatinine (μM)	88.4 ± 61.9	79.6 ± 35.4
Blood urea nitrogen (mM)	5.9 ± 1.8	5.5 ± 1.2
Glycosylated hemoglobin (%)	11.5 ± 2.9	12.8 ± 3.6

Values are means ± SE.

tion in steps of 1 Å. Each diameter-dependent urine/plasma fraction of dextran was corrected by the urine-plasma ratio of the GFR marker to obtain the sieving coefficient as a function of molecular diameter.

The analysis of glomerular permeability (K_f) was based on the use of a heteroporous model of the glomerular capillary as described previously (4,5). This model assumes the presence of restrictive cylinder pores with identical radius (r_o), which perforate the capillary wall. An additional parameter is given by the presence of a shunt pathway through which passes a small fraction of filtrate characterized as ω_o. The extent of this nondiscriminating pathway is a reflection of abnormal glomerular permeability. Permeability K_f reflects the product of hydraulic conductivity L_p and filtering glomerular area. The parameters are calculated independent of hemodynamic factors. Effective changes in urinary protein excretion follow from changes in hemodynamics and membrane permeability K_f, particularly radius r_o and alterations in the size of the shunt pathway.

Results are given as means ± SE. Analysis of variance and paired and unpaired *t* tests were used for statistical comparisons of groups. Placebo and active drug periods are compared. $P < 0.05$ was significant.

RESULTS

The protocol was well tolerated. One patient had an episode of ketoacidosis during the first treatment period. The patient finished this period (placebo) but declined to go into the crossover phase (ACE). One patient developed a mild dry cough during the 2nd trial period (ACE). This patient finished the study. This experience of adverse effects is in keeping with that reported elsewhere (6). There were no other side effects. There were no treatment effects on basic laboratory values (Table 2). Review of questionnaires at the end of each phase on the quality of life revealed no difference between phases (7). An overall estimate of quality of life by visual analogue scale (from 0 to 10 is from very bad to excellent) showed no difference between treatment and placebo phase (data not shown).

Mean 24-h and casual blood pressure readings aregiven in Table 3. In paired comparisons of casual blood pressures, no difference could be found. In comparisons of mean ambulatory blood pressure, ACE inhibition diminished blood pressure overall, but this change in normotensive individuals did not quite reach the nominal level of significance. Captopril significantly lowered GFR but not RPF. Both remained in the normal range (Table 4). Filtration fraction decreased significantly by 30% compared with placebo. ACE inhibition also lowered 24-h AER ($P < 0.1$) both with direct measure and after logarithmic conversion (Table 4). Reduction was related to the extent of albuminuria present at the outset ($r = 0.997$, $P < 0.001$). The association remained significant after logarithmic transformation ($r = 0.540$, $P < 0.02$). The effect of ACE on glomerular sieving characteristics for dextran is shown in Fig. 1. Sieving fraction was significantly reduced for a broad range of dextran molecules in the range of diameters between 23 and 60 Å. These changes in sieving coefficient are similar to those reported in patients with diabetes and more advanced nephropathy (8). The changes in calculated parameters of glomerular barrier function are summarized in Table 5. These calculations are based on the assumption of a net transmembrane hydraulic pressure gradient of 40 mmHg across the glomerulus during the placebo phase. With ACE therapy, we assumed a reduction in the gradient from 5 to 35 mmHg as described previously (8,9). Under these circumstances, there was a substantial reduction in effective pore radius r_o and a reduction in the nondiscriminatory shunt pathway ω_o. K_f was increased. These findings explain reduced proteinuria with ACE inhibition, particularly in the presence of reduced GFR. GFR was decreased despite K_f being increased. Because systemic blood pressure decreased only slightly, we assume that the ACE effect was expressed in the renal vascular bed alone, effectively lowering transglomerular pressure. However, we also calculated barrier parameters for a case of unchanged pressure gradients. In this case, there was a similar

TABLE 3
Effect of 25 mg b.i.d. captopril on casual blood pressure and mean ambulatory blood pressure

	Placebo	Captopril	*P*
Casual mmHg			
Systolic	120.8 ± 8.4	123.9 ± 2.4	NS
Diastolic	68 ± 5	72.5 ± 2.1	NS
24-h mean mmHg			
Systolic	126.0 ± 2.7	123.9 ± 2.4	0.08
Diastolic	74.2 ± 1.9	72.1 ± 1.9	0.09

Values are means ± SE.

TABLE 4
Effect of 25 mg b.i.d. captopril on renal function

	Placebo	Captopril	*P*
Glomerular filtration rate ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	99.5 ± 7.7	71.0 ± 5.5	0.0003
Renal plasma flow ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	443.9 ± 15.2	421.7 ± 17.5	NS
Filtration fraction (%)	22.4 ± 1.4	17.4 ± 1.4	0.006
Albumin excretion rate ($\mu g \cdot min^{-1} \cdot 1.73\ m^{-2}$)			
24 h	59.1 ± 29.8	27.7 ± 13.9	0.07
Log 24 h	1.24 ± 0.15	1.06 ± 0.12	0.09

Values are means ± SE.

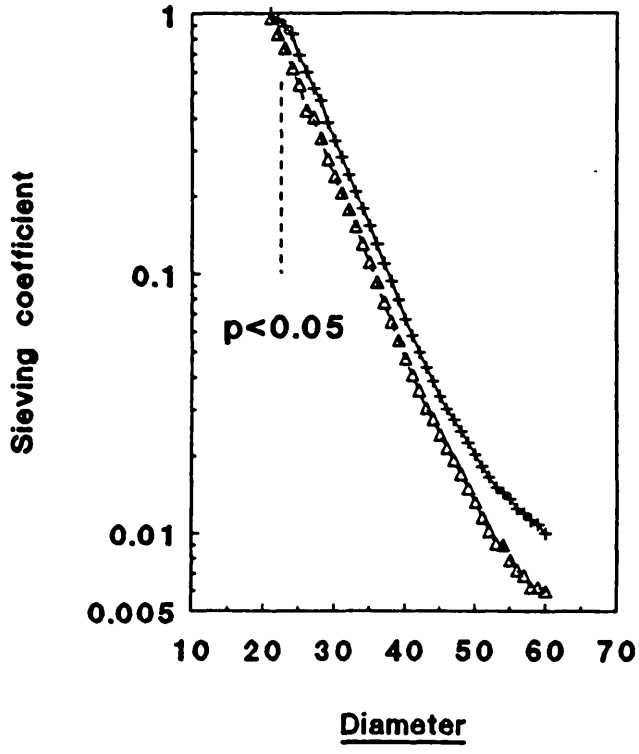

FIG. 1. Effect of angiotensin-converting enzyme (captopril) inhibition on dextran sieving coefficients in 18 normotensive patients with insulin-dependent diabetes mellitus. +, Placebo; △, captopril. Diameter is measured in ångströms.

decrease in r_o, and the decrease in the shunt fraction was somewhat smaller. Predictably, K_f was decreased.

DISCUSSION

Aggressive treatment of hypertension decreases the rate of deterioration of renal function in subjects with type I diabetes mellitus and overt diabetic nephropathy. Studies in patients with diabetes have focused on the use of ACE inhibitors because progression of renal failure has been linked to increase in intraglomerular capillary pressure (10) presumably due to angiotensin-induced constriction of the efferent glomerular arteriole. Treatment with ACE inhibitors over longer periods decreased the rate of progression of diabetic nephropathy as measured by GFR and albumin excretion (11). Renal function responses in acute studies are more variable, and ACE inhibition appears to elicit different responses, which may depend, among other factors, on type and extent of underlying disease and degree of hypertension.

These studies focus on the short-term use (<3 mo) of captopril in normotensive patients with type I diabetes. The purpose of these studies was to examine the effect of ACE inhibition on renal function (GFR and RPF) and glomerular permeability (dextran clearance). These patients did not have evidence of proliferative retinopathy, and 6 of 18 had urinary albumin excretion between 20 and 200 μg/min with the remainder <20 μg/min. The effect of ACE inhibition has not been studied in a controlled fashion in patients meeting these criteria. We found that the GFR, filtration fraction, and AER decreased significantly without major side effects. Moreover, abnormalities of glomerular capillary function parameters (permselectivity) were improved with ACE.

Short-term treatment with ACE inhibition in young normotensive patients with type I diabetes in these studies led to subtle changes in mean blood pressure averaged from 24-h ambulatory recordings. This change was not detectable by standard sphygmomanometery. This subtle change in blood pressure was accompanied by significant reduction in GFR within the normal range and no significant changes in RPF. Consequently, filtration fraction was significantly diminished. Urinary excretion of albumin was also diminished. These findings demonstrate that major changes in renal hemodynamic function may be found in the absence of equivalent changes in the systemic circulation.

These findings are consistent with other studies demonstrating net reduction in GFR with ACE inhibition. These findings in humans are consistent with the notion that angiotensin II primarily sustains net efferent glomerular resistance as originally described in isolated rabbit glomeruli (12). Angiotensin II in isolated rat kidney preparation increases GFR. Consequently, in the absence of other hemodynamic changes, we would expect a decrease in GFR during use of ACE inhibitors. These findings may be unique for younger patients at an early stage of the disease. The difference between these findings and previous studies in subjects with diabetes likely reflects the variety of other hemodynamic factors that may not be influenced by ACE inhibition in patients with more advanced degrees of vascular disease. For example, the patients in the study by Marre et al. (13) included both subjects with type I and non-insulin-dependent diabetes. Several subjects had proliferative retinopathy, and blood pressures were decidedly higher than in our study population. Likewise, the patients reported by Parving et al. (14) and those described by Morelli et al. (8) had more advanced nephropathy as defined by AER.

Angiotensin inhibition has been used previously in patients with diabetes. A decrease in GFR was not uniformly found. The short-term effects of captopril in normotensive subjects with incipient nephropathy have been examined and compared to the Ca^{2+} channel-blocker nifedipine (15–17). Use of ACE inhibition in these studies led to increased RPF and unchanged GFR. Consequently, there was a reduction in filtration fraction,

TABLE 5
Effect of angiotensin-converting enzyme inhibitor captopril (25 mg b.i.d.) on glomerular membrane parameters

	Placebo glomerular transmembrane pressure (mmHg)		Captopril glomerular transmembrane pressure (mmHg)	
	35	40	35	40
K_f (ml/min × mmHg)	13.2	7.7	8.6	5.2
r_o (Å)	49.8	50.8	47.4	48.6
ω_o	0.0042	0.0061	0.0030	0.0042

K_f, permeability; r_o, effective pore radius (Å); ω_o, shunt pathway.

which was thought to explain the significant decrease in AER. By comparison, nifedipine use led to similar increases in GFR and RPF, no change in filtration fraction, and increased AER. Short-term effects of enalapril have also been examined in proteinuric patients with type I diabetes who had evidence of proliferative retinopathy (8). Blood pressure was significantly reduced, albeit within the normal range, whereas there were no changes in GFR and RPF after 90 days of treatment.

ACE inhibitors have also been used chronically in subjects with type I diabetes who were normotensive. Marre et al. (13,18) compared responses to placebo and enalapril in patients with AER 20–200 μg/min. Treatment with ACE inhibitor over 1 yr prevented a decrease in GFR, whereas RPF was increased. Moreover, albuminuria decreased from baseline and remained at a lower level after 12 mo of treatment. Similar results were found by Parving et al. (14) in normotensive patients with AER >200 μg/min. Captopril slowed the rate of decline in GFR and interrupted the rise in AER over 1 yr. Other studies have examined the effect of ACE inhibition on exercise-induced proteinuria (17) or early stages of nephropathy (19). Chronic treatment in hypertensive subjects with diabetes decreased blood pressure and diminished albuminuria, whereas, GFR did not change appreciably. A moderate decrease in filtration fraction was attributed to increased RPF after ACE inhibition (11,20).

A variable hemodynamic response to ACE inhibition has been reported previously. The initial observations on the use of SQ 20881 in patients with essential hypertension demonstrated an increase in creatinine clearance (21), whereas, subjects with normal blood pressure had a small decrease within the normal range (22). On the other hand, patients with severe hypertension demonstrated significant reductions in GFR with blood pressure reduction due to short-term (9- to 12-wk) treatment with the ACE inhibitor cilazapril (23). Patients with variable degrees of hypertension and diminished renal function due to various proteinuric disease states had a significant 21% decrease in iothalamate clearance after 12 wk of treatment with lisinopril (24). A decrease in GFR was also seen in patients with type I diabetes treated with enalapril (19). In these patients, GFR appeared to decrease, especially in patients whose initial GFR was elevated (>130 ml/min). A moderate decrease in single-nephron GFR was also described originally by Zatz et al. (25) in their seminal observations on the use of enalapril in rats made diabetic with streptozocin. Our similar findings of decreased GFR do not indicate presence of renal disease. Rather, reduced GFR within the range of normal would be an expected functional and reversible hemodynamic response to ACE inhibition. Altogether, reduction of albuminuria with ACE inhibition may be the direct result of reduced GFR and filtration fraction in our patients.

Increasing proteinuria is also determined by glomerular permeability. This function of the glomerular barrier can be elucidated in vivo with dextran clearance (5). This technique determines size-dependent fractional clearances of a dispersed dextran mixture with variable molecular diameters compared to the marker for glomerular filtration, i.e., inulin. Fractional clearance as a function of molecular size is modeled for a glomerular barrier that is described by its effective glomerular pore size (r_o) and an additional shunt pathway (ω_o) for solute flow that bypasses filtration through the pores. This model is a mathematical approximation of glomerular barrier function rather than a descriptive morphological view.

Initial work in humans showed increased permeability and glomerular pore size in patients with diabetes mellitus. Subsequent work indicated reduced K_f and increased fractional size of the shunt compared with control subjects in diabetic nephropathy (26). Moreover, progressive impairment in size selectivity occurred over time. ACE inhibition may have altered glomerular permeability characteristics. For example, enalapril increased K_f in rats with renal ablation (27), with spontaneous glomerular sclerosis (28), and with streptozocin-induced diabetes (25). Enalapril also reduced the effective pore size of the basement membrane calculated from dextran clearance studies in sclerosing rat glomeruli (28). Use of enalapril in diabetic patients with advanced proteinuria and retinopathy resulted in significant changes of dextran sieving profiles (8). These changes were attributed to a change in r_o with little change in the nonspecific shunt pathway. Such studies have not been undertaken at an early stage of diabetes.

This study examined the barrier function of the glomerular basement membrane with the use of fractional dextran clearance measurements. Dextran sieving profile, baseline K_f, and r_o during the placebo phase were similar to those described in diabetic patients with nephropathy (8). On the other hand, the size of the nondiscriminatory shunt pathway was substantially larger and was similar to that described in a previous study of diabetic subjects (26) and patients with membranous glomerulopathy (29). Captopril altered dextran sieving characteristics over a wide range of molecular diameters accompanied by a decrease in effective r_o. These findings are similar to the aforementioned study in diabetic patients (8). In the absence of changes in GFR and plasma flow, the previous study was thought to best represent a reduction in albuminuria on the basis of change in intrinsic membrane properties. We also observed a substantial change in the fraction of glomerular filtrate escaping through a pore-size–independent pathway. This reduction in flow exceeded that seen in more advanced diabetic nephropathy (8). A similar reduction in shunt pathway size was also previously described after indomethacin therapy in patients with membranous glomerulopathy (29). Calculation of membrane characteristics depends on the extent of change in the transmembranous hydraulic pressure gradient. We, like others, did not measure the transmembrane hydraulic pressure gradient directly and assumed a reduction of 5 mmHg with ACE inhibition (8). ACE inhibition reduces effective hydraulic pressure by lowering net efferent glomerular resistance. This view is consistent with our finding of reduced GFR and filtration fraction after captopril therapy.

Reduction of proteinuria after captopril therapy appears to be the result of several additive factors. First, lowered GFR and filtration fraction should lower protein

excretion independent of change in glomerular barrier. Second, lowered transmembrane hydraulic pressures and GFR should also reduce pore size. Moreover, ACE inhibition reduced the shunt pathway. Thus, both hemodynamic and intrinsic renal parameters responded to ACE inhibition. This combination had not been found in previous studies of patients with diabetes but probably reflects differences in the age of patients, disease duration, current level of nephropathy, presence or absence and level of hypertension, systemic pressure response, and capillary responsiveness. Which of the many factors predominates remains to be established. We believe that individual capillary function may be of foremost importance. In any event, our results indicate that early treatment with ACE inhibition in patients with type I diabetes mellitus and mildly elevated albumin excretion results in favorable results with reduced AER. Were hyperfiltration present, it would be reduced, because GFR was diminished in this setting. Reduction of GFR within a normal range due to changes in hemodynamic conditions does not have the ominous significance of reduced function due to advanced nephron loss.

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