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Remission of nephrotic range proteinuria in type I diabetes

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Remission of nephrotic range proteinuria in type I diabetes. The present study assessed the extent to which remission of nephrotic-range proteinuria occurred in patients with Type I diabetes enrolled in the Captopril Study, a placebo controlled multicenter clinical trial of captopril therapy in diabetic nephropathy. Of the 409 patients recruited into the Captopril Study, 108 had nephrotic-range proteinuria (≥ 3.5 g/24 hr) at entry in the Study (baseline). This group was the subject of the present study. Remission of nephrotic-range proteinuria was defined as follows: (1) Onset of the remission was taken as the date when proteinuria was first noted to be ≤ 1.0 g/24 hr. (2) The reduction in proteinuria had to be sustained for a minimum of six months and until the end of the Captopril Study. (3) During the remission, the average of all 24 hour proteinuria measurements could not exceed 1.5 g. (4) Decline in renal function could not explain the reduced proteinuria. That is, the patient's serum creatinine during the entire period of observation in the Captopril Study had to remain at less than a doubling of the baseline serum creatinine. Remission of nephrotic-range proteinuria occurred in 7 of 42 patients assigned to captopril (16.7%, mean follow-up 3.4 ± 0.8 years) and in 1 of 66 patients assigned to placebo (1.5%, mean follow-up 2.3 ± 1.1 years; $P = 0.005$, comparing remission rate in captopril vs. placebo-treated patients). For those who achieved remission (Remission group), the mean baseline versus final proteinuria was 5.0 ± 2.0 versus 0.9 ± 0.7 g/24 hr ($P < 0.01$), and the mean baseline versus final serum creatinine was 1.5 ± 0.5 versus 1.6 ± 0.5 mg/dl (P = NS). For those who did not achieve remission (No remission group), the mean baseline versus final proteinuria was 6.2 ± 2.6 versus 5.1 ± 3.0 g/24 hr ($P < 0.01$), and baseline versus final serum creatinine was 1.5 ± 0.4 versus 3.2 ± 2.2 mg/dl ($P < 0.001$). Glomerular filtration rate (GFR) assessed by urinary iothalamate clearance was stable within the Remission group but declined significantly within the No remission group. During the Captopril Study, the Remission group did not differ from the No remission group with respect to diastolic blood pressure, glycohemoglobin level, or cholesterol level. However, mean systolic blood pressure during the Captopril Study was lower in the Remission group compared to the No remission group (126 ± 8 vs. 140 ± 13 mm Hg, $P = 0.002$). We conclude that long-term remission of nephrotic-range proteinuria with stable or nearly stable serum creatinine level is a realistic goal in Type I diabetes. Remission is significantly associated with captopril therapy and with achieving a lower systolic blood pressure.

It is widely believed that the onset of nephrotic-range proteinuria in the diabetic heralds the onset of inexorable progression to end-stage kidney failure [1]. This belief was tested in the NIH multicenter, controlled trial of captopril therapy in patients with Type I diabetes and nephropathy (the Captopril Study). The Captopril Study provided an unprecedented opportunity to examine the outcome of Type I diabetics with nephrotic-range proteinuria because of the large number of these patients enrolled (N = 108) and followed long term (median 2.7 years).

Methods

The present study is a subgroup analysis of patients recruited into the Captopril Study who at entry into the Study (baseline) had nephrotic-range proteinuria (24 hr proteinuria ≥ than 3.5 g). The Captopril Study was a prospective, double-masked, randomized clinical trial performed in 30 clinical centers with support by a Clinical Coordinating Center, a Central Laboratory, and a Biostatistical Coordinating Center. Entry criteria for the Captopril Study were patients aged 18 to 49 years, who had the onset of insulin-dependent diabetes before age 30, and had diabetes of at least seven years duration. In addition, the patients were required

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to have 24 hour proteinuria ≥ 500 mg and diabetic retinopathy. Patients with serum creatinine levels at baseline > 2.5 mg/dl were excluded. Details of the inclusion and exclusion criteria of the Captopril Study have been previously reported [2].

Patients accepted into the Captopril Study were randomized to captopril 25 mg three times daily or an identical placebo three times daily, as previously described [2]. Blood pressure goals were to achieve: (1) seated office diastolic pressure < 90 mm Hg; (2) seated office systolic blood pressure < 140 mm Hg, or if baseline systolic blood pressure was ≥ 150 mm Hg, the goal was a decrease of at least 10 mm Hg and a maximum systolic blood pressure of 160 mm Hg. These goals had to be achieved without the use of calcium channel blockers or other angiotensin-converting enzyme (ACE) inhibitors. Following randomization the patients were seen at two weeks, one month, and every three months thereafter until death, dialysis, or transplantation. The final status of patients with respect to death, dialysis, or renal transplantation was determined as of the date of administrative censoring on September 30, 1992.

Definitions used in the present study

Captopril Study patients with baseline nephrotic-range proteinuria (≥ 3.5 g/24 hr) were categorized based on their final outcome in the Captopril Study, as follows:

Remission of nephrotic-range proteinuria. Onset of the remission was defined as the date when 24 hour proteinuria was first noted to be ≤ 1 g. In addition the reduction in proteinuria had to be sustained for at least six months and until the end of the Captopril Study. During the period of remission the mean of all 24 hour proteinuria values could not exceed 1.5 g. Finally, the remission of nephrotic-range proteinuria could not be explained by decline in renal function. That is, during the course of the Captopril Study serum creatinine levels had to be maintained at less than a doubling of the baseline serum creatinine level, which was the primary study endpoint [2].

No remission of nephrotic-range proteinuria. This outcome was defined as failure to reduce proteinuria, as described above and/or failure to maintain serum creatinine at less than a doubling of baseline levels.

Statistical analysis

The results were analyzed with the Statistical Analysis System software [3]. Dichotomous baseline characteristics of the treatment groups and the remission groups were compared with Fisher's exact test [4]; continuous baseline characteristics and the mean value of measurements over follow-up visits were compared between the groups with Wilcoxon rank-sum test [5]. The change from baseline to the last follow-up visit within a remission group was assessed with Wilcoxon sign-rank tests [5]. The analyses included all patients with nephrotic syndrome at randomization with patients retained in their assigned treatment group regardless of their adherence to the treatment regimen. P value of less than 0.05 was considered to indicate statistical significance; all statistical tests were two-sided. Mean values are shown ± one standard deviation.

Results

The 30 clinical centers of the Captopril Study entered 409 patients into the study between December, 1987, and October, 1990. Of the 409 patients entered into the Captopril Study, 108 had nephrotic-range proteinuria at baseline. The baseline clinical characteristics of these patients according to assignment to the placebo or captopril group are shown in Table 1. As can be seen, the two groups were similar except that the percent of black patients (P = 0.025), and the urinary iothalamate clearance (P = 0.048) were higher in the placebo group than in the captopril group.

Table 1. Baseline clinical characteristics of the patients in this study who at baseline had nephrotic-range proteinuria and were then randomly assigned to the placebo or captopril groups

	Placebo group[a] (N = 66)	Captopril group[a] (N = 42)
Age	34.6 ± 6.5	34.9 ± 6.1
% Male	64	57
% Black	21	5
Body weight *kg*	75.8 ± 17	72.6 ± 14
Edema, *% of group*	52	50
Years of insulin therapy	20.5 ± 5.4	19.7 ± 6.0
Serum creatinine *mg/dl*	1.5 ± 0.4	1.6 ± 0.4
Creatinine clearance *ml/min*	72 ± 34	68 ± 38
I-GFR *ml/min*[b]	70 ± 33	59 ± 31
Proteinuria *g/24 hr*	5.9 ± 2.5	6.4 ± 2.7
Glycohemoglobin % (Normal up to 8%)	12.3 ± 3.3	12.5 ± 3.5
Serum cholesterol *mg/dl*	279 ± 75	300 ± 100
Serum albumin *g/dl*	3.3 ± 0.5	3.3 ± 0.5
Hematocrit %	38.1 ± 5.9	37.6 ± 4.9
Blood pressure *mm Hg*		
Systolic	144 ± 22	146 ± 18
Diastolic	88 ± 13	89 ± 9
MAP[c]	107 ± 14	108 ± 11
Pulse *beats/min*	83.0 ± 11	85.9 ± 9

[a] No significant differences were present at baseline between the patients with nephrotic-range proteinuria assigned to placebo or captopril, except for % black (P = 0.025) and I-GFR (P = 0.048)

[b] Urinary iothalamate (I) clearance (GFR) was performed in 64 of the placebo patients and 41 of the captopril patients at baseline

[c] Mean arterial pressure = diastolic pressure + 1/3 (systolic pressure − diastolic pressure)

Table 2 shows the baseline data on the 108 patients according to whether remission or no remission of nephrotic-range proteinuria occurred during follow-up in the Captopril Study. As can be seen, eight patients experienced remission, 100 patients did not. Seven of the eight patients who achieved remission during the Captopril Study had been assigned to captopril therapy. The remission rate associated with captopril therapy (16.7%) was 11 times greater than that associated with placebo therapy (1.5%), P = 0.005. Of the 16 black patients, none experienced remission of nephrotic-range proteinuria (P = 0.602).

Figure 1 shows the sequential changes in proteinuria and Figure 2 shows the sequential changes in serum creatinine in each of the eight Remission patients. As can be seen, each Remission patient maintained stable or nearly stable serum creatinine levels as proteinuria declined during the Captopril Study. The one patient assigned to placebo who achieved remission also received ACE inhibitor therapy for the majority of follow-up in the Captopril Study. This occurred when the patient was removed from the study protocol after 12 months because of inadequate control of blood pressure. At that time therapy with an ACE inhibitor was begun. This patient's course in relation to ACE inhibitor therapy is shown in more detail in Figures 1 and 2.

Table 2. Selected baseline characteristics of the patients who during the Captopril Study either achieved remission of nephrotic range proteinuria (Remission group) or did not achieve remission of nephrotic-range proteinuria during the Captopril Study (No remission group)

	Remission group, $N = 8$	No remission group, $N = 100$
Assignment[a]		
captopril	7	35
placebo	1	65
Age	34.1 ± 5.4	34.7 ± 6.5
% Male	62	61
% Black	0	16
Body weight *kg*	69.2 ± 9.5	75.0 ± 16.5
Edema, *% of group*	50	51
Years of insulin therapy	19.3 ± 6.8	20.3 ± 5.6
Serum creatinine *mg/dl*	1.5 ± 0.5	1.5 ± 0.4
Creatinine clearance *ml/min*	84 ± 41	69 ± 25
I-GFR	70 ± 39	66 ± 33
Proteinuria *g/24 hr*	5.0 ± 2.0	6.2 ± 2.6
Serum albumin *g/dl*[b]	3.6 ± 0.7	3.2 ± 0.5
Glycohemoglobin %	11.8 ± 2.8	12.4 ± 3.4
Serum cholesterol *mg/dl*	330 ± 200	284 ± 71
Hematocrit %	37.9 ± 6.4	37.9 ± 5.5
Blood pressure *mm Hg*		
systolic	135 ± 25	145 ± 20
diastolic	87 ± 18	89 ± 11
MAP	103 ± 19	108 ± 12
Pulse *beats/min*	90 ± 9	84 ± 11

[a] $P = 0.005$ comparing frequency of remission of nephrotic syndrome, during the Captopril Study, in captopril vs. placebo-treated patients. Five patients (2 assigned to captopril, 3 assigned to placebo) had 3 months or less follow-up in the Captopril Study. Baseline results for these patients are not included in the No remission group.

[b] $P = 0.048$

Table 3 summarizes the average of all follow-up laboratory and clinical parameters, and the final laboratory and clinical parameters, in the Remission and No remission groups. Five of the 108 patients with nephrotic-range proteinuria at baseline were not included in this analysis (2 assigned to captopril, 3 assigned to placebo) because only three months or less of follow-up data were available. For the eight patients who achieved remission, the clinical and laboratory characteristics did not change significantly from baseline (Table 2), except for proteinuria ($P = 0.008$) and cholesterol ($P = 0.039$). Relative to baseline, final proteinuria decreased by 4.1 ± 2.4 g/24 hr and cholesterol decreased by 127 ± 184 mg/dl. For the 95 patients who did not achieve remission and had at least three months of follow-up, all of the clinical and laboratory characteristics changed significantly from baseline (Table 2) except for glycosylated hemoglobin and systolic blood pressure. Relative to baseline, body weight, serum albumin and serum creatinine at the final visit increased while the clearance measurements, proteinuria, cholesterol, hematocrit, diastolic blood pressure and pulse rate decreased.

The distribution of the average of the sequential measurements at follow-up visits was compared between the remission groups. The average of the proteinuria measurements was significantly lower in the Remission group, $P < 0.001$. In addition, compared to the No remission group, the Remission group had significantly higher serum albumin levels ($P = 0.001$) and lower systolic blood pressures ($P = 0.002$).

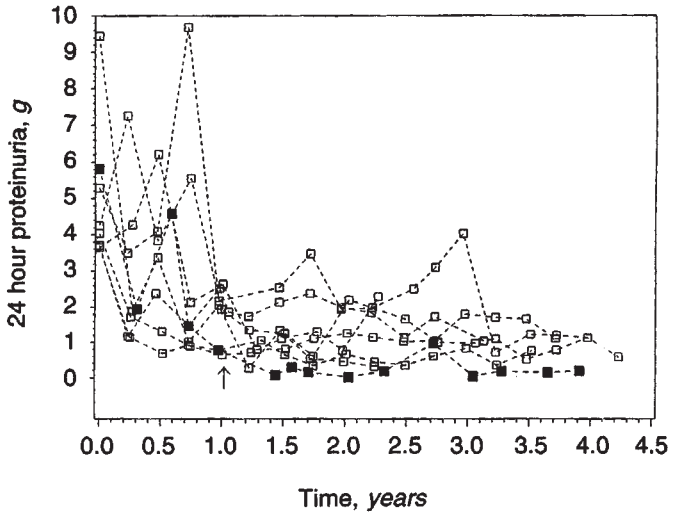

Fig. 1. *Sequential changes in 24-hour urine proteinuria in all patients (N = 8) who achieved remission of nephrotic-range proteinuria in the Captopril Study.* The study drugs (captopril or placebo) were begun at 0 years. The single patient assigned to placebo therapy is shown as a closed square. The point at which ACE inhibition therapy was begun in this patient is shown by an arrow.

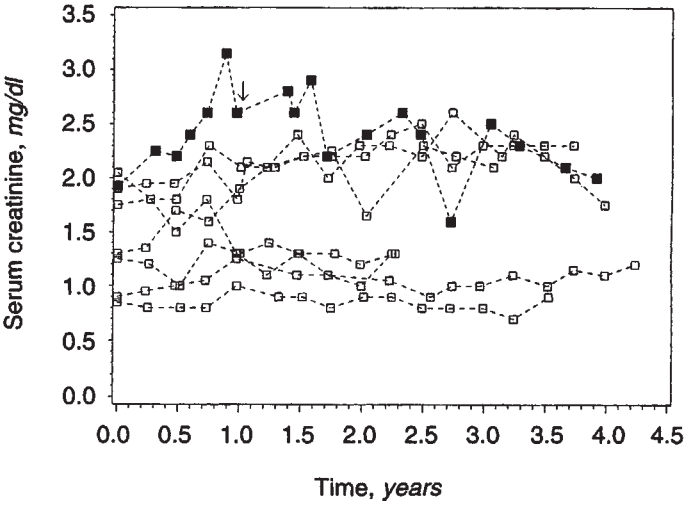

Fig. 2. *Sequential changes in serum creatinine in all patients (N = 8) who achieved remission of nephrotic-range proteinuria during the Captopril Study.* The conventions used in this figure are the same as those of Figure 1.

To assess whether the relationship between treatment assignment and remission was the result of a significantly greater number of blacks assigned to placebo ($N = 14$) versus captopril ($N = 2$), we evaluated the relationship between treatment assignment and remission in the subgroup of 92 non-black patients. This analysis showed that the remission rate associated with captopril therapy (17.5%, 7 of 40) was nine times greater than the placebo therapy remission rate (1.9%, 1/52), $P = 0.019$.

To assess whether differences in antihypertensive therapy, in addition to captopril, could account for remission of nephrotic-range proteinuria, we analyzed whether the use of diuretic, beta blocker, or clonidine therapy during the Captopril Study differed

Table 3. Summary of mean value of measurements at follow-up visits, and the last follow-up visit in the Remission group compared to No remission group

	Remission group (N = 8)		No-remission group (N = 95)	
Follow-up *years*	3.4 ± 0.8		2.3 ± 1.1	
	All follow-up	Final	All follow-up	Final
Body weight *kg*	68.0 ± 10.2	68.0 ± 10.1	75.4 ± 16.6	75.8 ± 17.1
Serum creatine *mg/dl*	1.6 ± 0.6	1.6 ± 0.5	2.4 ± 1.2	3.3 ± 2.2[a]
Clearance of creatinine *ml/min*	63 ± 35	67 ± 51	49 ± 28	38 ± 29[b]
I-GFR		59 ± 39		39 ± 28[c]
24 hr proteinuria *g*	1.6 ± 0.8	0.9 ± 0.7[d]	5.2 ± 2.3	5.1 ± 3.0
Serum albumin *g/dl*	4.0 ± 0.4	4.0 ± 0.5	3.3 ± 0.5	3.4 ± 0.6[e]
Glycohemoglobin %	11.5 ± 1.8	11.4 ± 2.0	12.5 ± 2.9	12.3 ± 3.2
Cholesterol *mg/dl*	242 ± 85	203 ± 29[f]	259 ± 61	238 ± 64
Hematocrit %	37.5 ± 5.5	36.9 ± 3.7	36.1 ± 5.6	34.0 ± 6.9
Blood pressure *mm Hg*				
systolic	126 ± 8[g]	119 ± 7	140 ± 13	143 ± 23
diastolic	81 ± 8	76 ± 7	85 ± 8	85 ± 11
MAP	96 ± 7[h]	90 ± 7	104 ± 8	104 ± 13
Pulse rate *per min*	81.1 ± 9.8	83.5 ± 20.8	82.2 ± 9.2	81.2 ± 10.5

[a] $P < 0.001$ compared to own baseline, $P = 0.018$ compared to other group Final value
[b] $P < 0.001$ compared to own baseline, $P = 0.048$ compared to other group Final value
[c] $P < 0.001$ compared to own baseline (75 of 95 patients studied)
[d] $P < 0.008$ compared to own baseline, $P < 0.001$ compared to other group Final value
[e] $P = 0.004$ compared to other group Final value
[f] $P = 0.039$ compared to own group baseline value
[g] $P = 0.002$ compared to other group Follow-up value
[h] $P = 0.013$ compared to other group Follow-up value

between the Remission and No remission groups. No significant differences of usage of these drugs was present, although there was a trend for more prevalent use of diuretics (mainly furosemide) in the No remission group in which 77.9% received a diuretic on 50% or more of scheduled visits. In the Remission group 50% received diuretics on 50% or more of scheduled visits ($P = 0.095$ comparing diuretic use in the Remission, No remission groups).

Dietary protein intake assessed by measurement of 24 hour urine urea excretion was not different between the Remission and No remission groups at baseline (14.1 ± 6.8 vs. 10.7 ± 5.3 g/kg/24 hr, $P = 0.144$) or during follow-up (9.9 ± 3.2 vs. 9.4 ± 3.7 g/kg/24 hr, $P = 0.616$).

Discussion

The present study demonstrates that patients with Type I diabetes and nephrotic-range proteinuria do not necessarily inexorably progress to renal failure, as the current literature suggests. Indeed, the present study demonstrates a relatively high rate of remission of nephrotic-range proteinuria that is accompanied by stable or nearly stable GFR over a mean follow-up period of 3.4 years (range 2.2 to 4.2 years).

The overall remission rate of nephrotic-range proteinuria in the Captopril Study was 7.4% (8 of 108 patients). However, the remission rate was 16.7% (7 of 42 patients) in those assigned to captopril therapy and 1.5% (1 of 66 patients) for those assigned to placebo therapy. The remission rate for the captopril group was significantly better than that of the placebo group ($P = 0.005$).

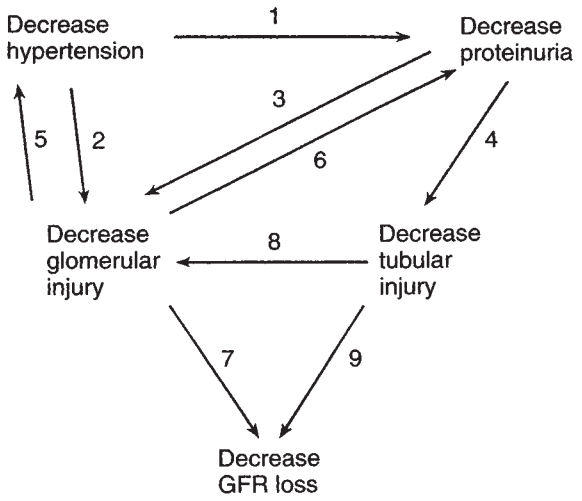

Fig. 3. *Possible interactions of hypertension, proteinuria, and GFR loss in patients with glomerulopathy.* The interactions are shown as numbered arrows. It is proposed that arrows 1 through 4 represent primary effects of the interactions. Arrows 5 through 9 represent secondary effects of the interactions. The relative importance of these primary and secondary effects are unknown.

The more favorable outcome in the captopril-treated patients with nephrotic-range proteinuria is consistent with the overall results of the Captopril Study [2]. That is, of the 409 patients entered into the Captopril Study, 207 patients were randomized to captopril and 202 patients were randomized to placebo therapy. During the course of the Captopril Study, 25 patients in the captopril group doubled their serum creatinine, compared to 43 patients in the placebo group ($P = 0.007$). It was also determined that the more favorable renal outcomes in the patients receiving captopril therapy could not be attributed to better blood pressure control. Thus, it was concluded that captopril exerts a renoprotective effect in Type I diabetes that is independent of the effect of captopril to lower blood pressure [2].

The patients in the present study who achieved remission of nephrotic-range proteinuria and maintained stable renal function, had significantly lower systolic blood pressure than those who did not achieve remission of nephrotic-range proteinuria. There is considerable evidence that control of blood pressure is important in decreasing proteinuria in patients with diabetic glomerulosclerosis [1, 6–8]. Thus, it is likely that at least some of the reduction in proteinuria in the Remission group can be attributed to better control of blood pressure in those receiving captopril therapy. On the other hand, there is considerable evidence that, at the same level of blood pressure control, ACE inhibitors are better at reducing proteinuria in diabetic patients than are other classes of antihypertensive agents [9]. Thus, it is also likely that at least some of the effect of captopril therapy to induce remission of nephrotic-range proteinuria, can be attributed to the fact that captopril is an ACE inhibitor.

A detailed analysis of the interrelationships between blood pressure, proteinuria, GFR loss, and its relevant covariates will be the subject of a separate report. However, it is appropriate to point out the complexities of these interrelationships (Fig. 3). We

suggest that both blood pressure control and reduced proteinuria contribute to the reduced rate of GFR loss in the Remission group compared to the No remission group. Evidence that blood pressure control may be a primary event (arrows 1 and 2) in slowing the progression of diabetic microvascular disease is suggested by the studies showing that the progression of diabetic nephropathy is slowed by measures that improve control of blood pressure [1, 6–8]. Evidence that reducing proteinuria may be a primary event (arrows 3 and 4) in slowing progression of renal disease is suggested by studies in experimental models of proteinuria and studies in humans [10]. These studies indicate that filtered proteins or substances accompanying the filtered proteins, may cause injury to the glomerular mesangium or epithelium, or to the renal tubules [11]. Nephrotoxic substances that are increased in glomerular filtrate under proteinuric conditions include the iron in transferrin, which may catalyze the formation of free oxygen radicals [12], lipids or lipoproteins that may activate inflammatory pathways [10], and components of the alternative complement pathway which can be activated by proximal tubular brush border [13]. Also, there is evidence in diabetics that the extent to which proteinuria is reduced by improving blood pressure control predicts the extent to which GFR decline is slowed [14].

Reductions in proteinuria may also slow progression of diabetic glomerulosclerosis because reducing proteinuria lowers plasma lipoproteins that can promote glomerular injury [15–17]. Captopril might also slow progression of diabetic glomerulosclerosis by effects not directly related to its effect to decrease proteinuria and decrease blood pressure. Recently it has been demonstrated that angiotensin II formation, which is inhibited by captopril, stimulates formation of TGF-β which induces collagen formation [18, 19]. Angiotensin II is also a growth factor that could promote glomerular hypertrophy, and its adverse effects on glomerular structure [20]. Both of these effects would be inhibited by captopril. Finally, captopril may have direct effects [21–24] or indirect effects [25] on the glomerular filtration barrier that could reduce proteinuria.

Previous studies do not show the high rates of remission of nephrotic-range proteinuria in patients with Type I diabetes, which are documented in the present study. However, the Captopril Study represents, by far, the largest number of patients with Type I diabetes and nephrotic-range proteinuria reported to date. Also, the average duration of therapy in the Captopril Study (median 2.7 years) is much longer than that of most previous studies involving ACE inhibition in diabetic glomerulosclerosis [1, 6, 9]. This is relevant because as demonstrated herein, the nadir levels of proteinuria in those who experienced remission generally occurred after one year of captopril therapy (Fig. 1).

The relatively high remission rate of nephrotic-range proteinuria in the present study might also be related to better blood pressure control achieved in the Remission group (mean follow-up systolic and diastolic blood pressure 126 ± 8 and 81 ± 8 mm Hg, respectively) compared to the No remission group (mean follow-up systolic and diastolic pressure 140 ± 13 and 85 ± 8 mm Hg, respectively). These observations suggest that in patients with diabetic glomerulosclerosis and nephrotic-range proteinuria, "hyper control" of blood pressure is important in slowing progression of diabetic renal disease. However, as suggested in Figure 3, decreased hypertension could also result from decreased glomerular damage. Thus, the present findings do not differentiate the effect of improved blood pressure control to lessen glomerular damage from the effect of less glomerular damage to improve blood pressure control.

Whether "hyper control" of blood pressure might cause harm in patients with diabetic glomerulosclerosis cannot be determined from the present study. There is evidence that patients with ischemic heart disease may be exposed to an increased risk of fatal myocardial infarction if their diastolic blood pressure is consistently reduced to less than 85 mm Hg [26]. In the Captopril Study we did not identify instances where myocardial ischemia was induced by achieving lower blood pressure levels. However, until studies examining the risk/benefit ratio of "hyper control" of blood pressure in patients with diabetic glomerulosclerosis are completed, no firm recommendations regarding specific levels of blood pressure control can be made.

Previous studies have demonstrated that reducing dietary protein intake in patients with diabetic glomerulosclerosis may reduce proteinuria and slow progression of renal disease [27] and that ACE inhibitor therapy and reduced protein intake may have additive beneficial effects on proteinuria [28]. However, these potential effects of diet cannot explain the present findings because there was no difference in dietary protein intake between the Remission and No remission groups during the Captopril Study, based on measurement of 24-hour urine urea excretion.

In summary, remission of nephrotic-range proteinuria, while maintaining stable or nearly stable renal function, is a realistic goal in patients with Type I diabetes and nephropathy. Captopril therapy and control of systolic blood pressure appear to be important in achieving this goal.

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