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Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy

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Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. Initiation of antihypertensive treatment (AHT) in hypertensive insulin-dependent diabetic (IDDM) patients with diabetic nephropathy (DN) induces a faster initial (0 to 6 months) and a slower subsequent (6 months to end of observation) decline in GFR [ΔGFR (ml/min/month) approximately 1.5 vs. 0.35]. Whether this initial phenomenon is reversible (hemodynamic) or irreversible (structural damage) after prolonged AHT is not known. To elucidate these mechanisms we investigated 42 hypertensive IDDM patients (16F/26M, age 40 ± 7 years, mean ± SD) with DN receiving AHT (angiotensin converting enzyme inhibition, $N = 30$) for 6 (2 to 15) years [median (range)]. GFR (ml/min/1.73 m^2), arterial blood pressure (BP, mm Hg) and albuminuria (mg/24 hr) were measured the last day on AHT and one month after withdrawal of AHT. The measured variables were all significantly elevated after withdrawal of AHT: GFR [mean(SEM)] from 76(4) to 81(4) ($P < 0.0001$), BP [mean(SEM)] from 140/82 (2/1) to 151/89 (2/1) ($P < 0.0005$) and albuminuria [geometric mean(antilog SEM)] from 704 (1.2) to 1122 (1.2) ($P < 0.0001$). A correlation between relative rise in systolic blood pressure (ΔSys%) and relative change in GFR (ΔGFR%) was found ($r = 0.44$, $P < 0.005$). Our results render some support of the hypothesis that the faster initial decline in GFR is due to a functional (hemodynamic) effect of AHT, which does not attenuate over time, while the subsequent slower decline reflects the beneficial effect on progression of diabetic nephropathy.

Nearly 40% of all insulin-dependent diabetic (IDDM) patients develop persistent albuminuria, a relentless decline in glomerular filtration rate (GFR), and raised arterial blood pressure (BP), that is, the clinical syndrome of diabetic nephropathy [1]. Elevated BP accelerates the progression of diabetic nephropathy [2–4] and effective antihypertensive treatment (AHT), in particular with angiotensin converting enzyme inhibitors (ACEI), reduces albuminuria and the rate of decline in GFR in this condition [5–9]. Initiation of AHT induces a faster initial (0 to 6 months) and slower subsequent (6 months to end of observation) decline in GFR [ΔGFR (ml/min/month) approximately 1.5 vs. 0.35] in hypertensive IDDM and non-insulin dependent diabetic (NIDDM) patients with incipient or overt diabetic nephropathy [7, 8, 10]. The same phenomenon has been recorded in the "Modification of diet in renal disease" (MDRD) study dealing with non-diabetic nephropathies [11–13]. Whether this initial faster decline in GFR is caused by a functional (hemodynamic) effect, which will not attenuate over time, or if it reflects an irreversible phenomenon (structural damage) is unknown. These mechanisms must be revealed in order to make a valid interpretation of the potential beneficial effect of long-term AHT on the progression of diabetic and non-diabetic nephropathies.

Our study aimed to elucidate this concept by recording the effect of withdrawing AHT on BP, GFR and albuminuria in IDDM patients with diabetic nephropathy receiving long-term AHT.

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Methods

Patients

Forty-two (16 females/26 males) consecutive hypertensive IDDM patients with diabetic nephropathy, who accepted to participate in a double blinded, randomized trial comparing lisinopril and nisoldipin (cc) were studied before the start of this trial. Diabetic nephropathy was diagnosed clinically if the following criteria were fulfilled: persistent albuminuria above 300 mg/24 hr, presence of diabetic retinopathy and no clinical or laboratory evidence of other kidney or renal tract disease, other than diabetic glomerulosclerosis [14]. All patients had been insulin-dependent from the time of diagnosis and all were receiving at least two daily injections of insulin. Diabetic retinopathy was evaluated by fundus photography after pupillary dilatation and graded: none, simplex or proliferative. All patients had received AHT for at least two years. Thirty patients were treated with an ACEI either alone ($N = 5$) or in combination with diuretics ($N = 24$) and/or a calcium channel blocker ($N = 8$) and/or a selective β-blocker ($N = 3$) and/or an α-blocker ($N = 2$). Twelve patients were treated with diuretics alone ($N = 5$) or in combination with either a calcium channel blocker ($N = 5$) and/or a selective β-blocker ($N = 4$) and/or an α-blocker ($N = 2$). Patients were excluded if they had a previous history of stroke/TIA, congestive heart failure (NYHA III-IV), myocardial infarction or coronary bypass surgery within the last three months and/or unstable angina. All patients were between 18 and 55 years of age. Characteristics of the 42 hypertensive IDDM patients with diabetic nephropathy are given in Table 1. The study was approved by the Regional Ethics Committee.

Table 1. Clinical characteristics of 42 hypertensive IDDM patients with diabetic nephropathy receiving long-term antihypertensive treatment (> 2 years)

Sex (F/M)	16/26
Age *(years)*[a]	40 (7)
Duration of diabetes *(years)*[a]	26 (6)
HbA_{1c} *(%)*[a]	9.0 (1.3)
Insulin dosage *(U/kg/day)*[a]	0.63 (0.14)
Duration of antihypertensive treatment *(years)*[b]	6 (2–15)
Duration of persistent albuminuria *(years)*[b]	6 (2–19)
Retinopathy (simplex/proliferative)	14/28

[a] Mean (SD)
[b] Median (range)

Table 2. Arterial blood pressure (BP), mean arterial blood pressure (MAP), GFR and albuminuria in 42 hypertensive IDDM patients with diabetic nephropathy, at baseline (last day of long-term antihypertensive treatment) and four weeks later without any antihypertensive treatment

	Baseline	4 weeks	*P*
BP *(mm Hg)*[a]	140/82 (2/1)	151/89 (2/1)	< 0.0005
MAP *(mm Hg)*[a]	101 (1)	109 (1)	< 0.0001
GFR *(ml/min/1.73 m^2)*[a]	76 (4)	81 (4)	< 0.0001
Albuminuria *(mg/24 hr)*[b]	704 (1.2)	1122 (1.2)	< 0.0001

[a] Mean (SEM)
[b] Geometric mean (antilog SEM)

Procedure

On the last day of AHT (baseline) and four weeks after withdrawal of all antihypertensive drugs BP, GFR and albuminuria were determined. All patients received placebo in the four week period.

All investigations were performed with the patients in the supine position between 8 a.m and 1 p.m. The investigations were started in the morning after an overnight fast. Patients had breakfast and morning insulin 30 minutes after the start of the GFR investigation and drank approximately 200 ml of tap water per hour during the investigation period. GFR was measured after a single intravenous injection of 3.7 MBq $Na^{51}Cr$-labeled edetic acid (^{51}Cr-EDTA) at 8 a.m., by determining the radioactivity in venous blood samples 180, 200, 220 and 240 minutes after the injection [15, 16]. The small underestimation (10%) of ^{51}Cr-EDTA clearance versus clearance of inulin was corrected for by multiplying the EDTA clearance by 1.10 [15]. The results were standardized for 1.73 m^2 body surface area. The mean coefficient of variation in GFR is 4% in our laboratory.

In 34 patients linear regression analysis (least squares method) was used to estimate the rate of decline in GFR during the AHT period previous to the present investigation by using all determinations of GFR (range: 2 to 9) over a period of time of 31 (13 to 121) months [median(range)]. The rate of decline in GFR could not be determined in the remaining eight patients, because of insufficient numbers of GFR measurements or a short observation period (less than 12 months).

BP was measured on the right arm after at least 10 minutes rest in the supine position with a Hawksley random zero sphygmomanometer, using appropriate cuff sizes [25 × 12 cm (upper arm circumference ≤ 35 cm) and 30 × 15 cm (upper arm circumference > 35 cm)]. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase V). The individual BP level was determined as the mean of at least two measurements performed during the GFR determination. Albuminuria was determined by using an enzyme linked immunoadsorbent assay [17]. From venous blood samples hemoglobin A_{1c} (HbA_{1c}) was measured by high performance liquid chromatography (DIAMAT analyzer, BIO-RAD, CA, USA). The normal range of HbA_{1c} in our laboratory is 4.1 to 6.4%.

Statistical analysis

Normally distributed data are expressed as mean and standard deviation (SD) or standard error of the mean (SEM). Duration of persistent albuminuria and duration of AHT are expressed as median and range owing to their skewed distribution. Values for albuminuria were logarythmically transformed before analysis and expressed as geometric mean and antilog SEM, because of their positively skewed distribution. Paired Student's *t*-test was used to compare BP, GFR and albuminuria at baseline and four weeks after withdrawal of AHT in the whole group of patients. Unpaired Student's *t*-test was used to compare ACEI and non-ACEI treated patients, relating to baseline values of MAP, GFR and albuminuria and changes in mean arterial blood pressure (MAP), GFR and albuminuria from baseline (visit 0) to four weeks after (visit 4) withdrawal of AHT. Change in albuminuria is expressed as the mean relative change (%) with 95% confidence interval, from visit 0 to visit 4. Linear regression analysis (least squares method) was used to analyze data for correlations. All calculations were made using Statgraphics (STSC, Rockville, MD, USA). A *P* value of < 0.05 was considered significant (two-tailed).

Results

BP, GFR and albuminuria were all significantly elevated after withdrawal of long-term AHT (Table 2). Figures 1, 2 and 3 illustrate the individual changes in mean arterial blood pressure (MAP), GFR and albuminuria, from baseline (on AHT) to the visit four weeks after withdrawal of all antihypertensive drugs, respectively.

Thirty-two patients had an increase in MAP (ACEI, $N = 22$), while eight had a drop in MAP (ACEI, $N = 6$). On average the increase amounted to 8 (1) mm Hg (Fig. 1).

GFR rose in 32 patients (ACEI, $N = 24$), while 8 patients (ACEI, $N = 5$) had a slight reduction in GFR. The mean increase was 5(1) ml/min/1.73 m^2 (Fig. 2). The increase in GFR was not related to the baseline GFR level.

Albuminuria rose in 34 patients (ACEI, $N = 26$) and decreased in seven patients (ACEI, $N = 4$) after withdrawal of AHT (Fig. 3).

Our study revealed no significant differences in the change of MAP, GFR and albuminuria after four weeks withdrawal of ACEI ($N = 30$) compared to non-ACEI ($N = 12$) in hypertensive IDDM patients suffering from diabetic nephropathy. However, the rise in albuminuria tended to be higher in the ACEI versus the non-ACEI group, 71% versus 34%, but the numbers were small (Table 3).

Linear regression analysis revealed a significant correlation between relative change in systolic blood pressure (ΔSys%) and relative change in GFR (ΔGFR%; $r = 0.44$, $P < 0.005$); (Fig. 4). Compared to the whole group of patients there was a slightly better correlation between ΔSys% and ΔGFR% in patients receiving ACEI ($r = 0.50$, $P < 0.005$). Furthermore, a significant correlation between relative change in MAP (ΔMAP%) and ΔGFR% ($r = 0.34$, $P < 0.05$) was also found. We found no

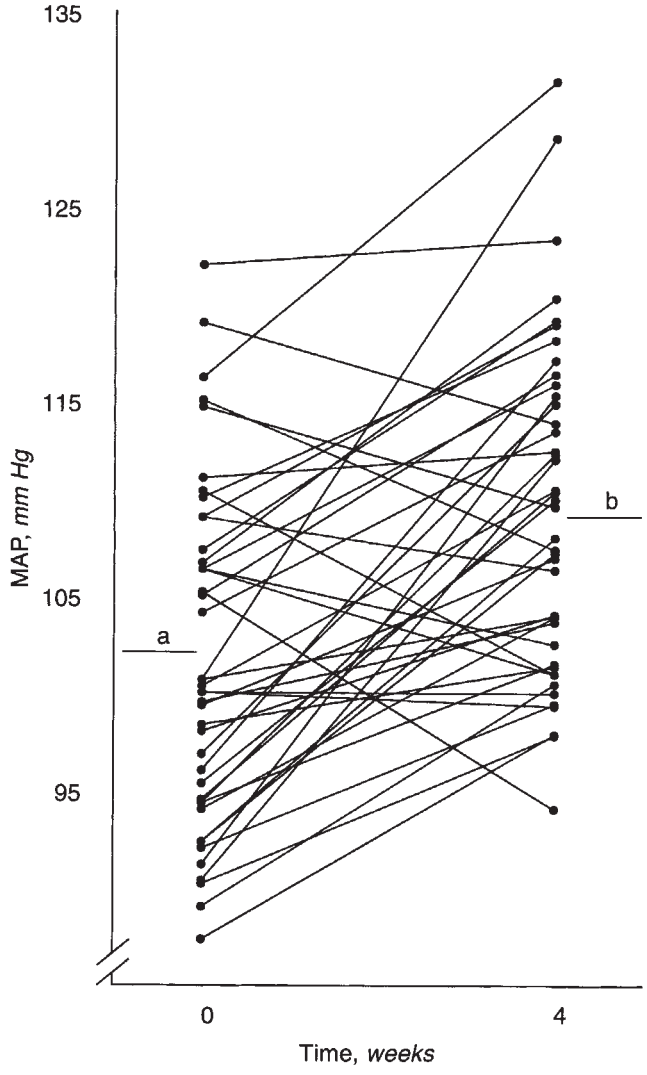

Fig. 1. *Mean arterial blood pressure (MAP) at baseline [last day of long-term antihypertensive treatment (AHT)] and four weeks after withdrawal of long-term AHT, in 42 hypertensive IDDM patients with nephropathy.* Thirty-two patients had a rise in MAP and eight patients dropped in MAP. **A.** Average MAP (101 mm Hg) at baseline, and **B.** average MAP (109 mm Hg) four weeks after withdrawal of AHT ($P < 0.0001$).

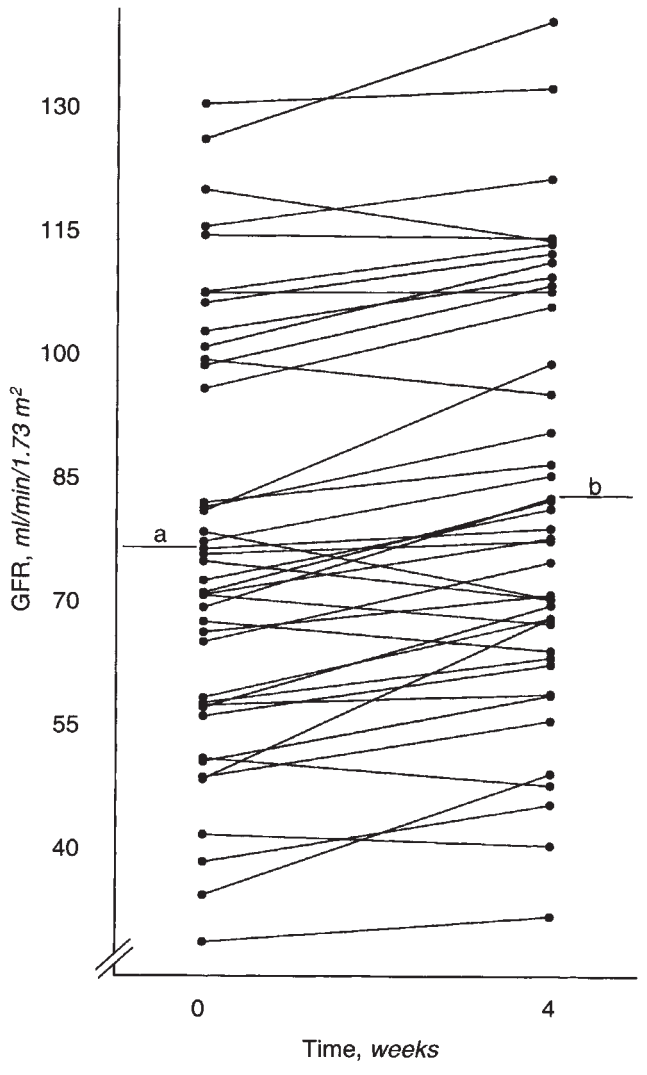

Fig. 2. *GFR at baseline [last day of long-term antihypertensive treatment (AHT)] and four weeks after withdrawal of AHT, in 42 hypertensive IDDM patients with diabetic nephropathy.* Thirty-two patients had an increase in GFR and eight patients had a decline in GFR. **A.** Mean GFR at baseline (76 ml/min/1.73 m^2), and **B.** mean GFR four weeks after withdrawal of AHT (81 ml/min/1.73 m^2; $P < 0.0001$).

correlation between duration of antihypertensive treatment and absolute change in GFR ($r = 0.10$, $P > 0.5$; Fig. 5), and no correlation between the relative change in systolic blood pressure and relative change in albuminuria ($P > 0.1$), or between relative change in GFR and relative change in albuminuria ($P > 0.2$).

The rate of decline in GFR during the AHT period preceding the present investigation was 3.5 (−8 to 27) ml/min/year [median(range)].

Discussion

Our prospective study shows that short-term withdrawal (one month) of long-term antihypertensive treatment (years) induces a rise in BP, GFR and albuminuria in hypertensive IDDM patients suffering from diabetic nephropathy. It should be mentioned that some variation in the response occurred, since 20 to 25% of the patients had an unchanged or decrease in BP and/or GFR and/or albuminuria, respectively. Correlations between ΔSys% and ΔGFR% and between ΔMAP% and ΔGFR% were demonstrated. No correlation was found between the absolute change in GFR and duration of antihypertensive treatment, suggesting that the capability to increase GFR after withdrawal of long-term antihypertensive treatment does not attenuate over time. Finally our study demonstrates that the yearly rate of decline in GFR (3.5 ml/min) during long-term antihypertensive treatment is low as compared to approximately 12 ml/min/year, reflecting the natural course of diabetic nephropathy [6, 18].

Recently, Apperloo et al [19] have demonstrated that the initial decline in GFR induced by antihypertensive treatment can be regained after short-term withdrawal of this treatment in 36 proteinuric non-diabetic patients (GFR > 30 ml/min/1.73 m^2), treated for 3.8 years with atenolol or enalapril in a double-blind trial (code has still not been broken).

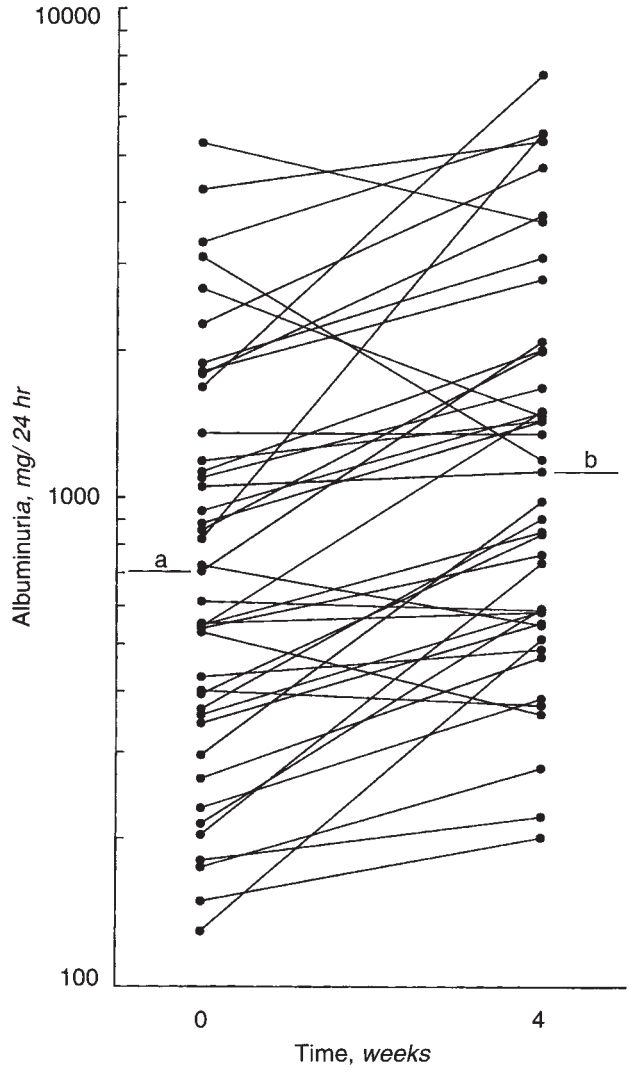

Fig. 3. *Albuminuria at baseline [last day of long-term antihypertensive treatment (AHT)] and four weeks after withdrawal of long-term AHT, in 42 hypertensive IDDM patients with diabetic nephropathy.* Albuminuria rose in 34 patients and dropped in 7 patients. **A.** Geometric mean albuminuria (704 mg/24 hr) at baseline, and **B.** geometric mean albuminuria (1122 mg/24 hr) four weeks after withdrawal of AHT (log scale; $P < 0.0001$).

The effect of pharmacological blood pressure lowering and/or reduction of dietary protein intake on the rate of decline in GFR can best be fitted to a two-slope model, with a faster initial (during the first 4 to 6 months) and a slower sustained (6 months to end of observation) decline in GFR of approximately 1.5 and 0.35 ml/min/month, respectively [7, 8, 10]. This phenomenon has been demonstrated in IDDM and NIDDM patients with incipient or overt diabetic nephropathy and in non-diabetic nephropathies [7, 8, 10, 11]. The initial rapid loss of GFR may represent either a destruction of nephrons (progression in renal disease), or it may reflect a functional hemodynamic effect of low blood pressure and/or low protein diet intervention without a loss of nephrons. In case the first mentioned event takes place, then the initial drop in GFR has to be accounted for, when evaluating the long-term effect of intervention on progression of kidney disease. However, if the initial steeper drop in GFR is hemodynamically induced (reversible) then only the sustained effect on GFR, reflecting progression of the renal disease, should be analyzed in long-term intervention trials. Several recent studies lasting at least 2½ years shows a beneficial effect of AHT and/or low protein diet in diabetic and non-diabetic nephropathies, if and only if the sustained effect on GFR is analyzed [5, 11, 20].

The MDRD study randomly assigned patients with moderate renal insufficiency to a usual- or a low-protein diet and to a usual- or a low-blood pressure group [11]. As compared with the usual-protein group and the usual-blood pressure group, the low-protein group and the low-blood pressure group had a more rapid decline in GFR during the first four months after randomization and a slower decline thereafter. The effect of the dietary intervention was similar in the two blood pressure groups, and the effect of the blood pressure intervention was similar in the two diet groups.

The initial drop in GFR after four months of AHT is about 6 ml/min in diabetic nephropathy and our study revealed a regain in GFR of the same order of magnitude after one month of withdrawal of AHT, which may suggest a reversible hemodynamic effect. Unfortunately, we have no data prior to and shortly after the initiation of antihypertensive treatment in our patients. Furthermore, our study cannot rule out the possibility that the initial hemodynamically-mediated decline in GFR had attenuated over time and yet, the diabetic kidney, retained the ability to respond to a relatively acute increase in BP with an increase in GFR.

The physiological determinants of GFR are: The ultrafiltration coefficient (K_f), the transcapillary hydraulic pressure difference ($\Delta\bar{P}$) and the transcapillary oncotic pressure difference ($\Delta\bar{\pi}$). We have no direct information on these variables. However, we found a correlation between ΔSys% and ΔGFR% and between ΔMAP% and ΔGFR%. Systemic blood pressure elevation is only of importance for the regulation of GFR if it is transmitted downstream to the glomeruli, resulting in glomerular hypertension. This is likely to occur since the autoregulation of GFR [or intraglomerular hydraulic pressure ($\bar{P}_{GC}$)], that is, the maintenance of relative constancy of GFR (or P_{GC}) despite variations in mean arterial blood pressure above 80 mm Hg [21–25], is impaired in diabetic nephropathy [26]. A complete pressure-passive vasculature has been found in 30% of the patients with diabetic nephropathy (ΔGFR% = ΔMAP%) [26]. Impaired autoregulation of renal blood flow (RBF) and GFR has also been found in experimental models of non-diabetic nephropathies [27–29]. The renin-angiotensin system has been suggested to play a role in the autoregulation of GFR [30]. However, angiotensin II antagonists failed to interfere with renal autoregulation in the majority of studies performed [31–33].

Inhibition of the angiotensin converting enzyme prevents the action of angiotensin II on mesangial cells and the efferent arteriole, thereby enhancing K_f and reducing the $\bar{P}_{GC}$ irrespective of the effect on systemic hypertension. Consequently withdrawal of ACE inhibition should induce a reduction in K_f, offsetting the enhancing effect of glomerular hypertension on GFR. The net result of these opposing variables in our study was an increased GFR. We have no information suggesting that conventional antihypertensive drugs have specific effects on the above-mentioned determinants of GFR, but β-blockers may reduce renal blood flow. No difference in the rise of GFR after withdrawal of ACEI and non-ACEI was found, but the numbers of patients

Table 3. Changes in MAP, GFR and albuminuria after four weeks withdrawal of angiotensin converting enzyme inhibitors (ACEI) versus non-ACEI in 42 hypertensive IDDM patients with diabetic nephropathy

	MAP[a] *mm Hg*			GFR[a] *ml/min/1.73 m²*			Albuminuria mg/24 hr[b]		%[c]
Antihypertensive treatment	Visit 0	Visit 4	Δ	Visit 0	Visit 4	Δ	Visit 0	Visit 4	Δ
ACEI (N = 30)	102 (2)	110 (2)	8 (2)	78 (5)	84 (5)	6 (1)	682 (1.2)	1166 (1.2)	71 (40 to 209)[d]
Non-ACEI (N = 12)	100 (3)	108 (2)	8 (2)	72 (6)	77 (5)	5 (2)	762 (1.3)	1019 (1.3)	34 (−5 to 88)[d]

[a] Mean (SEM)
[b] Geometric mean (antilog SEM)
[c] Average relative change (%) from visit 0 to 4 with 95% confidence interval
[d] P = 0.21 compared to ACEI

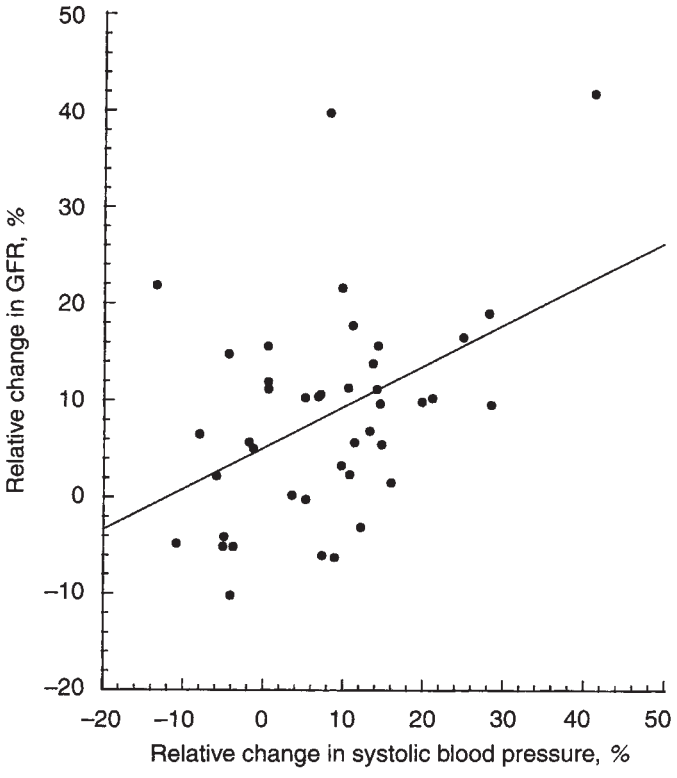

Fig. 4. *Correlation between relative change in systolic blood pressure (ΔSys%) and relative change in GFR (ΔGFR%) in 42 hypertensive IDDM patients previously receiving long-term antihypertensive treatment* (r = *0.44*, P < *0.005*).

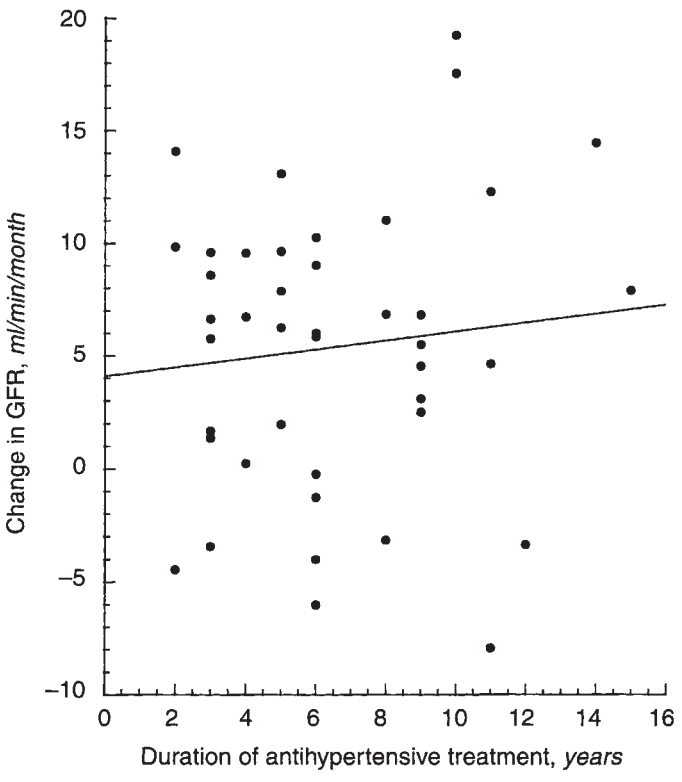

Fig. 5. *No correlation between duration of antihypertensive treatment and absolute change in GFR (ΔGFR;* r = *0.10*, P > *0.5) was found.*

studied were small, particularly in the non-ACEI group. Unfortunately, we have no data on plasma oncotic pressure during and after withdrawal of AHT, but we do not expect significant changes in $\Delta\bar{\pi}$.

Antihypertensive treatment with ACEI or non-ACEI reduces albuminuria in diabetic nephropathy [5–7, 18]. Given the same systemic blood pressure level, ACEI are usually more potent than non-ACEI in reducing albuminuria, suggesting a local effect on $\bar{P}_{GC}$ and/or a non-hemodynamic effect in the glomeruli. The rise in albuminuria after stopping antihypertensive treatment was nearly twice as high in the group treated with ACEI compared to the non-ACEI treated group (Table 3).

The size and charge selectivity of the glomerular capillary filtration barrier is impaired in patients with diabetic nephropathy [34]. Antihypertensive treatment with an ACEI has been shown to improve both size and charge selective properties [35]. Studies on the effect of acute blood pressure reduction with clonidin suggest that albuminuria in diabetic nephropathy is pressure dependent to a large extent [26]. These findings propose that the rise in albuminuria after withdrawal of antihypertensive treatment is probably due to both hemo- and non-hemodynamic mechanisms.

Studies concerning the effect of withdrawal of long-term antihypertensive treatment on BP, GFR and albuminuria in NIDDM patients with diabetic nephropathy and on albuminuria in patients with non-diabetic nephropathies are lacking.

In conclusion, our results render some support of the hypothesis that the faster initial decline in GFR after initiating antihypertensive treatment in hypertensive IDDM patients with diabetic

nephropathy is due to a hemodynamic effect, which does not attenuate over time. The subsequent slower decline in GFR reflects the beneficial effect of antihypertensive treatment on the progression of diabetic nephropathy.

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