Remission of Nephrotic-Range Albuminuria in Type 1 Diabetic Patients

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OBJECTIVE — To evaluate the cumulative incidence of nephrotic-range albuminuria (NRA), the frequency of remission, and the impact on progression, we analyzed data from a prospective cohort study of type 1 diabetic patients with diabetic nephropathy.

RESEARCH DESIGN AND METHODS — All of the albuminuric type 1 diabetic patients (n = 321, 121 women), who had at least yearly measurements of glomerular filtration rate (GFR) with a ^{51}Cr-EDTA plasma clearance technique and were followed for at least 3 years, were evaluated. NRA, defined as persistent albuminuria >2,500 mg/24 h, occurred in 126 patients (35 women) aged (mean ± SD) 34 ± 8 years, with duration of diabetes 22 ± 8 years and follow-up time from onset of NRA (median [range]) 8.7 (3.0–20.9) years. Remission of NRA was defined as sustained albuminuria <600 mg/24 h for at least 1 year.

RESULTS — The cumulative incidence of NRA was 39%. Remission was induced in 28 of 126 (22%) patients; 21 were predominantly treated with ACE inhibitors, 7 with non–ACE inhibitor medications. Remission lasted 3.6 (1.0–18.1) years. More women (37%) than men (16%) obtained remission (P = 0.01). In the remission group compared with the no-remission group, mean arterial blood pressure (mean ± SEM) was reduced (102 ± 1 vs. 106 ± 1 mmHg, P < 0.01), the rate of decline in GFR was diminished (3.8 ± 0.6 vs. 7.5 ± 0.5 ml · min^{-1} · year^{-1}, P < 0.001), and serum cholesterol was lower (5.3 ± 0.2 vs. 6.1 ± 0.1 mmol/l, P < 0.01) during the whole follow-up period. No difference in glycemic control was found between groups (HbA_{1c} 9.2 vs. 9.4%, NS).

CONCLUSIONS — In contrast to observations made before the use of antihypertensive treatment, our prospective observational study suggests that aggressive antihypertensive treatment with and without ACE inhibitors can induce long-lasting remission in a sizeable fraction of type 1 diabetic patients with NRA. The group of patients obtaining remission is characterized by slow progression of diabetic nephropathy and improved cardiovascular risk profile.

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Diabetic nephropathy is a chronic progressive kidney disease with high morbidity and mortality (1). The natural history of diabetic nephropathy, i.e., without antihypertensive treatment, is a progressive and irreversible course without recovery or cure (2) and is characterized by an early elevation of arterial blood pressure, increasing albuminuria, and a relentless mean decline in glomerular filtration rate (GFR) of ~10–12 ml · min^{-1} · year^{-1} (3–5). The degree of albuminuria is closely related to the progression of diabetic nephropathy, as previously reviewed by Rossing (6). Diabetic patients with nephrotic-range albuminuria (NRA) have the fastest decline in GFR (7) and the shortest survival time (2,8). Recently, Hebert et al. (9) have challenged the concept that a relentless progression is inevitable in all type 1 diabetic patients with nephrotic-range proteinuria. Remission, defined as a reduction of proteinuria from >3,500 mg per 24 h to <1,000 mg per 24 h, was demonstrated in some patients (8 of 108) with nephrotic-range proteinuria participating in the Collaborative Study Group multicenter controlled trial of captopril therapy in patients with type 1 diabetes and nephropathy (9).

To evaluate the cumulative incidence of NRA and the frequency of remission in a large population, we analyzed data from a long-term prospective observational study of 321 consecutive type 1 diabetic patients with diabetic nephropathy. The impact of remission on the rate of decline in GFR, measured yearly with a ^{51}Cr-EDTA plasma clearance technique, was assessed in the subset of 126 patients with NRA.

RESEARCH DESIGN AND METHODS

At the Steno Diabetes Center, we included all type 1 diabetic patients who had diabetic nephropathy and who had their kidney function monitored with at least one yearly determination of GFR and a minimum of 3 years follow-up, n = 321. The recruitment period for our prospective cohort study started in 1976 and ended in 1997. A subset of this cohort followed from 1983 has been previously described in detail (10). Diabetic nephropathy was diagnosed clinically if the following criteria were fulfilled: persistent albuminuria >300 mg/24 h in at least two of three consecutive 24-h urine collections, presence of diabetic retinopathy, and absence of any other evidence of kidney or renal tract disease (11). Nephrotic-range proteinuria has previously been defined as persisting proteinuria >3,500 mg/24 h, and remission of nephrotic-range proteinuria has been defined as a reduction to <1,000 mg/24 h (9). From 50 consecutive patients with diabetic nephropathy, a correction factor between albuminuria and proteinuria of 0.70 was determined from 24-h urine samples (all with albuminuria >1,000 mg/24 h) and applied.

Therefore, NRA was defined as persisting albuminuria >2,500 mg/24 h in at least two of three consecutive 24-h urine

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

collections. A significant threshold effect of albuminuria at ~600 mg/24 h on the rate of decline in GFR has previously been demonstrated (10). Remission of NRA was accordingly defined as a reduction in albuminuria from NRA to <600 mg/24 h, sustained for at least 1 year during the follow-up period.

Of the total cohort consisting of 321 patients (200 men and 121 women), NRA developed in 126 patients (91 men and 35 women) during follow-up. At onset of NRA (baseline), 67 patients (53%) were without antihypertensive treatment, 25 (20%) were treated predominantly with ACE inhibitors, and 34 (27%) patients were treated with antihypertensive agents other than ACE inhibitors. During follow-up, all 126 patients except one started antihypertensive treatment, 103 (82%) patients were treated predominantly with ACE inhibitors, and 22 (18%) were treated with other antihypertensive agents. Patients were classified as taking ACE inhibitors if this class of antihypertensive agents was prescribed before or during the individual's follow-up time. All patients took at least two daily injections of insulin and had a diabetic diet containing 45–55% carbohydrates, 30–35% fat, and 15–20% protein. No sodium or protein restrictions were applied during the study. Lipid-lowering treatment and aspirin were used as secondary prevention in patients with concomitant cardiovascular disease. During the whole follow-up period, we strived to keep blood pressure <140/90 mmHg. Of the patients, 14% received monotherapy, 44% received two agents, 35% received three agents, and 7% were treated with four or more antihypertensive drugs. The local ethics committee approved the experimental design, and all patients gave their informed consent.

Procedures

The measurement of GFR was performed 3–39 times (median 11) in each patient during a median follow-up period of 8.7 (3.0–20.9) years. GFR was measured after a single intravenous injection of 3.7 MBq ^{51}Cr-EDTA by determination of the radioactivity in venous blood samples taken 180, 200, 220, and 240 min after the injection (12). The mean variability in GFR of each patient from day to day was 4%. Results are standardized for 1.73 m^2 body surface, and throughout the study the patients' surface area at the start of the study was used.

Albuminuria was measured in 24-h urine collections as well as in timed urine collections obtained during the 4-h clearance period (10). HbA_{1c} was measured from venous blood samples by isoelectric focusing and high-performance liquid chromatography (10). The normal range was 4.1–6.4%. Serum cholesterol was measured with standard laboratory techniques. Arterial blood pressure was measured at each visit with a standard mercury sphygmomanometer and appropriate cuff size. The measurements were performed twice on the right arm, after at least 10 min rest in the supine position, and averaged. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase V). Arterial hypertension was diagnosed according to World Health Organization criteria (≥160/95 mmHg) until 1995, and thereafter it was diagnosed according to American Diabetes Association criteria (≥140/90 mmHg) (13). All patients visited the outpatient clinic every 3–4 months during the study. Blood glucose concentration, HbA_{1c}, albuminuria, blood pressure, and body weight were monitored, and the insulin dose and antihypertensive treatment were adjusted.

Retinopathy was assessed after pupillary dilatation by ophthalmoscopy, and from 1991 it was assessed by fundus photography and graded as follows: nil, simplex, or proliferative diabetic retinopathy.

Statistical analysis

Results are expressed as the means ± SEM, with the means ± SD being used for descriptive information. Albuminuria is given as median (range) and logarithmically transformed before analysis because of the positively skewed distribution. In each patient, all measurements performed during the entire follow-up period were used to calculate mean values. Linear regression analysis (least squares method) was used to determine the slope of GFR for each patient. In normally distributed variables, comparison between groups was performed by an unpaired Student's *t* test, and comparison within groups was performed by a paired *t* test. In nonnormally distributed continuous variables, a Mann-Whitney *U* test was used for comparison between groups. A χ^2 test was used to compare frequencies. Cox proportional hazards multiple regression analyses were performed to examine the baseline variables predictive of remission.

All calculations were performed with a commercially available program, SPSS 10.0 (SPSS, Chicago, IL).

RESULTS — Of the 321 consecutive type 1 diabetic patients with diabetic nephropathy, 39% (126) developed NRA, which was more frequent among men than women (91 of 200, 46% [95% CI 39–52], vs. 35 of 121, 29% [21–37]; $P < 0.01$). The demographic data and baseline clinical and laboratory values, calculated as the mean of values during the first year after onset of NRA, are shown in Table 1. The two groups were comparable, except for retinopathy: a larger proportion of the patients in the remission group had more severe retinopathy ($P < 0.05$).

Remission was obtained in 22% ($n = 28$) of the 126 patients with NRA. The average duration of remission was 3.6 (range 1.0–18.1) years. Of these 28 patients, 19 remained in remission to the end of follow-up, with a median follow-up period of 10.2 (7.0–20.9) years and a median duration of remission of 4.2 (1.0–18.1) years. However, nine patients relapsed from remission, with a median follow-up period of 11.8 (7.2–18.8) years and a duration of remission of 3.0 (1.0–12.2) years. Remission was less frequent in men than women (15 of 91, 17% [95% CI 9–24] vs. 13 of 35, 37% [21–53]; $P = 0.01$).

To analyze remission rates over time, all 126 patients with NRA were divided according to the median year (1988) of onset of NRA. The frequency of remission was 22% (14 of 63 patients) in each group (NS). Backward stepwise Cox multiple regression analysis showed that only the female sex was significantly and independently associated with remission of NRA (RR 2.9 [95% CI 1.3–6.2], $P = 0.007$), whereas baseline values of GFR, blood pressure, albuminuria, HbA_{1c}, calendar year and age at onset of NRA, smoking, and grade of retinopathy were not included in the model. Clinical and laboratory data during follow-up are presented in Table 2 and Fig. 1.

During the whole follow-up period, patients in the remission group had a significantly lower rate of decline in GFR compared with the no-remission group (3.8 vs. 7.5 ml · min^{-1} · $year^{-1}$, $P < 0.001$). In the remission group, 16 pa-

Table 1—*Baseline data in 126 type 1 diabetic patients with diabetic nephropathy and nephrotic-range albuminuria, showing values for those with or without remission*

Characteristic	Remission group	No-remission group
n	28	98
Sex (M/F)	15/13	76/22
Height (cm)	171 ± 9	173 ± 7
Age at onset of nephrotic-range albuminuria (years)	32 ± 7	35 ± 8
Age at onset of diabetes (years)	12 ± 7	12 ± 7
Retinopathy (simplex/proliferative)	2/26	27/71*
Smoking (yes/no)	12/16	57/41
GFR (ml · min^{-1} · 1.73 m^{-2}	78 ± 25	78 ± 24
Systolic blood pressure (mmHg)	146 ± 13	145 ± 15
Diastolic blood pressure (mmHg)	91 ± 8	89 ± 8
Mean arterial blood pressure (mmHg)	109 ± 8	108 ± 9
Albuminuria (mg/24 h)	2,593 (515–4,800)	2,670 (893–7,448)
HbA_{1c} (%)	9.0 ± 1.7	9.4 ± 1.3
Serum cholesterol (mmol/l)	6.6 ± 1.9	6.3 ± 1.3

Data are *n*, means ± SD, or medians (range). Nephrotic-range albuminuria was defined as persisting albuminuria >2,500 mg/24 h in at least two of three consecutive 24-h urine collections. Means of values during the first year after onset of nephrotic-range albuminuria are given. Consequently, some patients with persistent nephrotic-range albuminuria starting antihypertensive treatment had a mean urinary albumin excretion rate <2,500 mg/24 h during the first year. *$P < 0.05$ compared with the remission group.

tients had at least three measurements of GFR both before and during remission. In these patients, the rate of decline in GFR from the onset of NRA to remission was 5.6 ml · min^{-1} · year^{-1} compared with 0.8 ml · min^{-1} · year^{-1} during remission ($P <$ 0.001).

Of the 126 patients, all but 1 received antihypertensive treatment during the follow-up period. A significantly lower mean arterial blood pressure was demonstrated in the remission group compared with the no-remission group ($P < 0.01$). During antihypertensive treatment, 17 patients (61% [95% CI 43–79]) in the remission group and 33 patients (34% [24–44]) in the no-remission group achieved a mean systolic blood pressure <140 mmHg during the follow-up period ($P =$ 0.01). In the remission group, 26 patients (93% [84–100]) had an average diastolic blood pressure <90 mmHg during the follow-up period, compared with 69 patients (71% [62–80]) in the no-remission group ($P < 0.05$). In the remission group, 16 patients (57% [39–75]) met both blood pressure goals, compared with 32 patients (33% [24–42]) in the no-remission group ($P < 0.05$). Of the 28 patients obtaining remission, 21 were treated with ACE inhibitors, and 7 received non–ACE inhibitor treatment. The prevalence of remission was 20% (13–28) in the ACE inhibitor–treated group, compared with 32% (12–51) in the non–ACE inhibitor group (NS). In the patients not obtaining remission, those treated with an ACE inhibitor ($n = 82$) had received this treatment for 6.7 (range 0.1–14.9) years. Patients obtaining remission had received ACE inhibitors for 3.6 (0.5–11.5) years before remission. There was no difference between the remission and no-remission groups in terms of the distribution of the number of antihypertensive agents used during follow-up (NS).

Serum cholesterol during follow-up was lower in the remission group ($P <$ 0.01). In the remission group, five patients (18% [95% CI 4–32]) were treated with lipid-lowering agents, predominantly hydroxymethylglutaryl-CoA reductase inhibitors, compared with 18 patients (18% [11–26]) in the no-remission group (NS). No differences were demonstrated in glycemic control during follow-up, measured as HbA_{1c}, between patients obtaining remission and those not obtaining remission (9.2 vs. 9.4%, NS).

CONCLUSIONS — Our prospective observational study demonstrates that ~40% of a large unselected cohort of type 1 diabetic patients with diabetic nephropathy will develop NRA. However, as opposed to observations made before the use of antihypertensive treatment, long-lasting remission of NRA can be obtained in a sizeable fraction of these patients by aggressive antihypertensive therapy with

Table 2—*Clinical and laboratory data during the follow-up period in 126 type 1 diabetic patients with diabetic nephropathy and nephrotic-range albuminuria, showing values for those with or without remission*

	Remission	No remission	*P*
n	28	98	
Rate of decline in GFR during the entire observation period (ml · min^{-1} · year^{-1})	3.8 ± 0.6	7.5 ± 0.5	<0.001
Systolic blood pressure (mmHg)	140 ± 2.2	147 ± 1.2	<0.05
Diastolic blood pressure (mmHg)	83 ± 1.1	86 ± 0.6	<0.01
Mean arterial blood pressure (mmHg)	102 ± 1.1	106 ± 0.7	<0.01
Albuminuria (mg/24 h)	725 (68–2,247)	2,385 (820–7,420)	
HbA_{1c} (%)	9.2 ± 0.2	9.4 ± 0.1	NS
Serum cholesterol (mmol/l)	5.3 ± 0.2	6.1 ± 0.1	<0.01
Observation time (years)	11.0 (7.0–20.9)	7.8 (3.0–19.6)	<0.001

Data are means ± SEM or medians (range). In each patient, all measurements performed during the entire follow-up period were used to calculate mean/median values. Some patients with previously persistent albuminuria receiving antihypertensive treatment had urinary albumin excretion rates <300 mg/24 h.

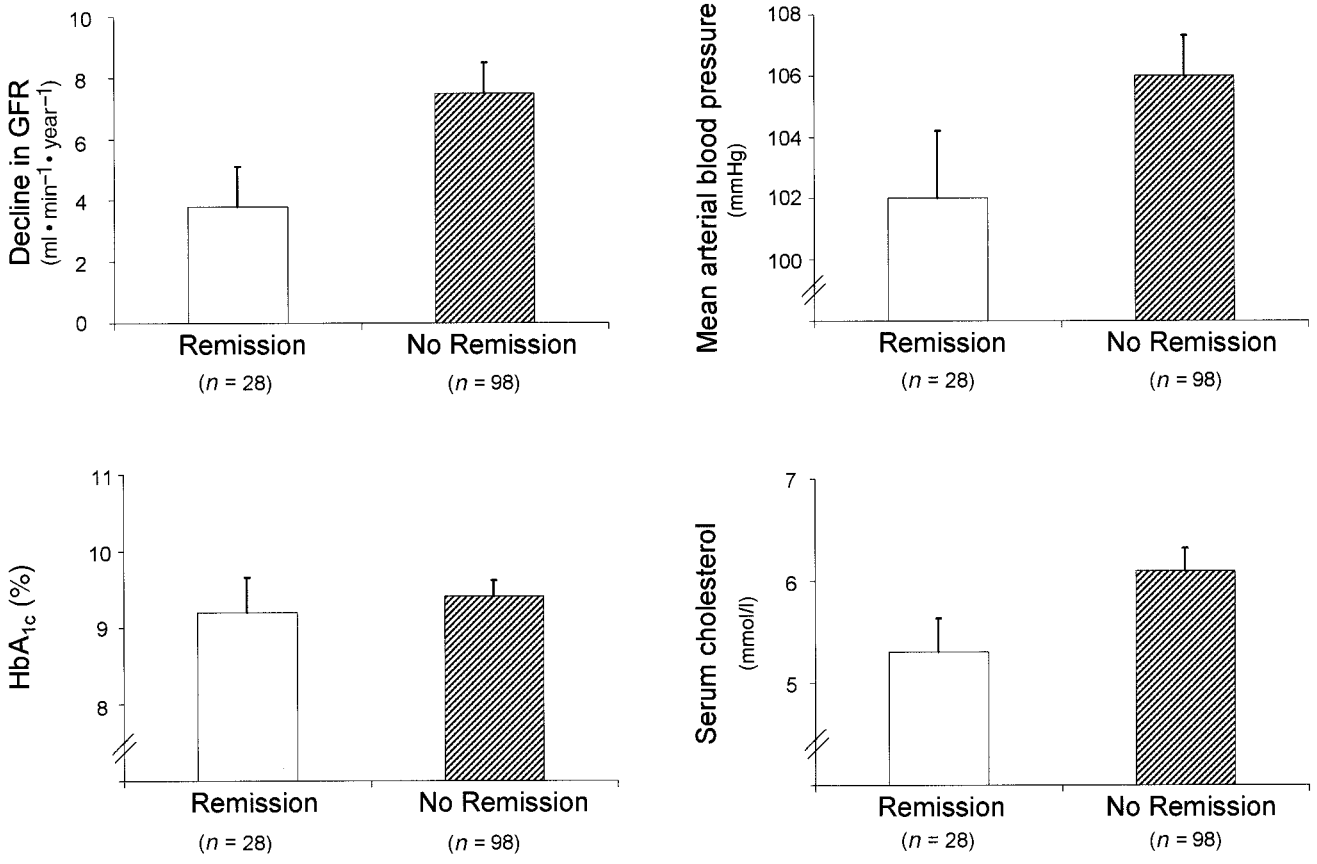

Figure 1—*Decline in GFR, mean arterial blood pressure, HbA_{1c}, and serum cholesterol during follow-up in 126 type 1 diabetic patients with diabetic nephropathy, showing values for those obtaining or not obtaining remission. Error bars represent 95% CI. Statistically significant differences were found between groups for decline in GFR* ($P < 0.001$), *mean arterial blood pressure* ($P < 0.01$), *and serum cholesterol* ($P < 0.01$).

and without ACE inhibitors. Apart from this treatment modality, no other major target organ–saving procedure was introduced during the follow-up period. In particular, no change in HbA_{1c} was observed between the groups. The remission group is characterized by a slow progression of diabetic nephropathy and improved cardiovascular risk profile.

In 1972, Watkins et al. (8) performed a follow-up study in proteinuric type 1 diabetic patients, identifying a subset of patients with a very poor prognosis. The patients with proteinuria >3,000 mg/24 h all died after 2–6 years of follow-up (8). Subsequently, Kussman et al. (2) conducted a retrospective analysis of records from 112 type 1 diabetic patients with diabetic nephropathy, demonstrating diabetic nephropathy to be a chronic, progressive, and irreversible disease with an accelerated loss in kidney function in the later stages. The progressive nature of diabetic kidney disease was confirmed in the present study, because 39% of a large cohort of type 1 diabetic patients with diabetic nephropathy followed for 3–21 years progressed to NRA. The observed cumulative incidence of NRA must be regarded as conservative, because initiation of antihypertensive treatment will reduce albuminuria, thereby reducing the risk of progression to NRA.

Long-term remission of nephrotic-range proteinuria, defined as remission from proteinuria >3,500 to <1,000 mg/24 h and sustained levels of <1,500 mg/24 h for at least 6 months, and stabilization of serum creatinine, was originally demonstrated by Wilmer et al. (14) during antihypertensive treatment with an ACE inhibitor in a small subset (6 of 103 patients) of type 1 diabetic patients with diabetic nephropathy. The remission rate was reported to be 16.7% in patients assigned to captopril treatment and 1.5% in the patients treated with conventional antihypertensive treatment. The nadir levels of proteinuria in those patients who obtained remission occurred after >1 year of follow-up (14). By applying comparable criteria in our long-term observational study, we demonstrated a remission rate of 22% for NRA. The observed frequency of remission must be regarded as conservative, because only 33% of the patients in the no-remission group treated with antihypertensive agents achieved a blood pressure <140/90 mmHg.

The male sex seems to be more susceptible to progression to diabetic NRA and more resistant to antihypertensive treatment. A more rapid decline in renal function has also been reported in men with nondiabetic renal disease (15). Testosterone has been found to be a permissive factor for renal compensatory growth in the model of uninephrectomy in rats, thereby possibly accelerating progression of renal disease in the male sex (16). We have no explanation for the observed more severe grade of retinopathy in patients obtaining remission, and we consider it to be a chance finding.

Numerous studies have documented the renoprotective effect of antihypertensive treatment (11,17–21). The patients

in the remission group, though having the same mean arterial blood pressure at onset of NRA, had significantly lower mean arterial blood pressure during follow-up. Remission did not occur spontaneously, but was induced by antihypertensive treatment with ACE inhibitors as well as other antihypertensive agents. This finding suggests that aggressive treatment of arterial hypertension can induce remission of NRA in type 1 diabetic patients. A renoprotective effect of ACE inhibitors above and beyond the effect of blood pressure lowering has been demonstrated in clinical trials (14,21,22). We could not confirm this finding in our long-term prospective observational study; however, our study was not designed to evaluate this concept.

Reduction in albuminuria is a surrogate parameter for the issue of importance: the rate of decline in GFR. Patients obtaining remission of NRA in the present study have a slower rate of decline in GFR, roughly a 50% reduction in progression, compared with patients not obtaining remission (3.8 vs. 7.5 ml · min^{-1} · $year^{-1}$). Furthermore, when decline in GFR was evaluated before and during remission, a significantly lower decline in GFR was found during remission, thus predicting a better outcome in terms of survival and survival free of end-stage renal failure.

Development of overt diabetic nephropathy has for many years been regarded as a "point of no return" in relation to glycemic control (6). Recent studies have found a significant impact of glycemic control on the progression of nephropathy (10,18,23,24) and the reversal of lesions of diabetic glomerulopathy (25). However, in the present study, we did not find an effect of improved glycemic control on remission.

Hyperlipidemia presumably has an impact on the progression of renal disease (10,26,27). In the present study, the patients in the remission group had a significant reduction in serum cholesterol during follow-up. Because there was no difference between the remission and the no-remission groups regarding lipid-lowering treatment in our study, the observed decrease in serum cholesterol is most likely attributable to a reduction in albuminuria. However, long-term trials applying a principal end point, such as a decline in GFR, are still lacking.

To improve the treatment and prognosis, it is important to analyze why some patients are responders, i.e., obtain remission, whereas others are nonresponders. Because well-known risk factors for the progression of diabetic kidney disease (i.e., arterial blood pressure, albuminuria, HbA_{1c}, and lipids) measured at the onset of NRA were similar in responders and nonresponders, other factors seem to play a part. Genetic factors of importance for the progression of diabetic nephropathy, e.g., the ACE I/D polymorphism, could possibly differentiate between the remission and the no-remission group. Unfortunately, DNA for genotyping was available in only a subset of the investigated patients. Variation in dietary salt intake and activity of the renin-angiotensin system could also contribute to the difference between responders and nonresponders.

The number of antihypertensive agents used in responders and nonresponders was similar. Because ours is an observational study, the compliance concerning adherence to prolonged antihypertensive treatment was not assessed. Previously, Caro et al. (28) found that 53% of the hypertensive patients treated with an ACE inhibitor and only 40% of the patients treated with diuretics were taking their prescribed medication after 5 years. Treatment with several antihypertensive agents, which is often necessary in diabetic nephropathy, may reduce compliance even further. Additionally, even at the same blood pressure level, nonadherence to treatment (e.g., ACE inhibitor therapy) will render the patients devoid of the nonhemodynamic beneficial effects of these compounds (21,22).

In summary, as opposed to observations made before the use of antihypertensive treatment, our prospective study suggests that aggressive antihypertensive treatment with and without ACE inhibitors can induce long-lasting remission in a sizeable fraction of type 1 diabetic patients with NRA. The remission group is characterized by slow progression of diabetic nephropathy and improved cardiovascular risk profile.

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References

1. Parving H-H, Østerby R, Ritz E: Diabetic nephropathy. In *The Kidney*. 6th ed. Brenner BM, Ed. Philadelphia, WB Saunders, 2000, p. 1731–1773
2. Kussman MJ, Goldstein HH, Gleason RE: The clinical course of diabetic nephropathy. *JAMA* 236:1861–1863, 1976
3. Mogensen CE: Progression of nephropathy in long-term diabetics with proteinuria and effect of initial antihypertensive treatment. *Scand J Clin Lab Invest* 36:383–388, 1976
4. Parving H-H, Smidt UM, Friisberg B, Bonnevie-Nielsen V, Andersen AR: A prospective study of glomerular filtration rate and arterial blood pressure in insulin-dependent diabetics with diabetic nephropathy. *Diabetologia* 20:457–461, 1981
5. Viberti GC, Bilous RW, Mackintosh D, Keen H: Monitoring glomerular function in diabetic nephropathy. *Am J Med* 74: 256–264, 1983
6. Rossing P: Promotion, prediction, and prevention of progression in diabetic nephropathy. *Diabet Med* 15:900–919, 1998
7. Austin SM, Lieberman JS, Newton LD, Mejia M, Peters WA, Myers BD: Slope of serial glomerular filtration rate and the progression of diabetic glomerular disease. *J Am Soc Nephrol* 3:1358–1370, 1993
8. Watkins PJ, Blainey JD, Brewer DB, Fitzgerald MG, Malins JM, O'Sullivan DJ, Pinto J: The natural history of diabetic renal disease: a follow-up study of a series of renal biopsies. *Q J Med* 41:437–456, 1972
9. Hebert LA, Bain RP, Verme D, Cattran D, Whittier FC, Tolchin N, Rhode RD, Lewis EJ: Remission of nephrotic-range proteinuria in type I diabetes. *Kidney Int* 46: 1688–1693, 1994
10. Hovind P, Rossing P, Tarnow L, Smidt UM, Parving HH: Progression of diabetic nephropathy. *Kidney Int* 59:702–709, 2001
11. Parving H-H, Andersen AR, Smidt UM, Svendsen PA: Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* i:1175–1179, 1983
12. Bröchner-Mortensen J: A simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Invest* 30:271–274, 1972
13. American Diabetes Association: Treatment of hypertension in diabetes (Consensus Statement). *Diabetes Care* 16: 1394–1401, 1993
14. Wilmer WA, Hebert LA, Lewis EJ, Rohde RD, Whittier F, Cattran D, Levey AS, Lewis JB, Spitalewitz S, Blumenthal S, Bain RP: Remission of nephrotic syndrome in type 1 diabetes: long-term follow-up of patients in the captopril study.

Am J Kidney Dis 34:308–314, 1999
15. Neugarten J, Acharya A, Silbiger SR: Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol* 11:319–329, 2000
16. Zeier M, Schonherr R, Amann K, Ritz E: Effects of testosterone on glomerular growth after uninephrectomy. *Nephrol Dial Transplant* 13:2234–2240, 1998
17. Parving H-H, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA: Effect of antihypertensive treatment on kidney function in diabetic nephropathy. *Br Med J* 294:1443–1447, 1987
18. Parving H-H, Smidt UM, Hommel E, Mathiesen ER, Rossing P, Nielsen FS, Gall M-A: Effective antihypertensive treatment postpones renal insufficiency in diabetic nephropathy. *Am J Kidney Dis* 22:188–195, 1993
19. Mathiesen ER, Borch-Johnsen K, Jensen DV, Deckert T: Improved survival in patients with diabetic nephropathy. *Diabetologia* 32:884–886, 1989
20. Rossing P, Hougaard P, Borch-Johnsen K, Parving H-H: Predictors of mortality in insulin dependent diabetes: 10 year follow-up study. *Br Med J* 313:779–784, 1996
21. Lewis E, Hunsicker L, Bain R, Rhode R: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456–1462, 1993
22. Björck S, Mulec H, Johnsen SA, Norden G, Aurell M: Renal protective effect of enalapril in diabetic nephropathy. *BMJ* 304:339–343, 1992
23. Mulec H, Blohmé G, Grände B, Björck S: The effect of metabolic control on rate of decline in renal function in insulin-dependent diabetes mellitus with overt diabetic nephropathy. *Nephrol Dial Transplant* 13:651–655, 1998
24. Nyberg G, Blohmé G, Nordén G: Impact of metabolic control in progression of clinical diabetic nephropathy. *Diabetologia* 30:82–86, 1987
25. Fioretto P, Steffes MW, Sutherland DER, Goetz FC, Mauer M: Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* 339:69–75, 1998
26. Moorhead JF, El-Nahas M, Chan MK, Varghese Z: Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. *Lancet* ii:1309–1311, 1982
27. Wheeler DC: Lipids—what is the evidence for their role in progressive renal disease? *Nephrol Dial Transplant* 10:14–16, 1995
28. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD: Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data [see comments]. *CMAJ* 160:41–46, 1999