Kidney International, Vol. 47 (1995), pp. 231–235

Effect of intensive treatment on diabetic nephropathy in patients with type I diabetes

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Effect of intensive treatment on diabetic nephropathy in patients with type I diabetes. We evaluated the long-term effect of an intensive treatment of diabetic nephropathy (anti-hypertensive drugs, low protein diet, multiple insulin injections to achieve a good metabolic control) on glomerular filtration rate (GFR) and albumin excretion rate (AER). Fourteen type I diabetic patients (mean age 45 ± 9.5 years, mean duration of diabetes 23.5 ± 7.3 years, 8 males/6 females) with glomerular filtration rate <70 ml/min^{-1}/1.73 m^2 and albumin excretion rate >30 μg/min were treated intensively for 36 months. This intensive treatment consisted of multiple insulin injections, antihypertensive therapy with ACE inhibitors and a low-protein diet (0.8 g/kg body wt/day.) Renal function was evaluated as GFR and AER. HbA_1c mean value decreased significantly from 8.7 ± 0.8% to 6.5 ± 0.5% ($P < 0.0002$). GFR rose from 58 ± 12 ml/min^{-1}/1.73 m^2 to 84 ± 11 ml/min^{-1}/1.73 m^2 ($P < 0.0008$). AER decreased from 208 μg/min (range: 73 to 500) to 63.8 μg/min (range 15 to 180; $P < 0.05$). Systolic and diastolic blood pressure decreased respectively from 144 ± 26 mm Hg to 120 ± 15 mm Hg and from 89 ± 9 mm Hg to 75 ± 8 mm Hg ($P < 0.01$). We obtained a rise of GFR and a reduction of proteinuria after three years of this treatment. We suggest that this intensive treatment in all patients with early stage diabetic nephropathy may be effective in slowing the progression to renal failure.

Diabetic nephropathy is defined by a progressive decline in glomerular function until end-stage renal failure and is characterized by persistent albuminuria >300 mg/24 hr, decline in glomerular filtration rate and often raised blood pressure [1–4]. The presence of proteinuria is not simply a marker of the extent of glomerular damage but proteinuria *per se* may contribute to renal lesions. This complication which is the single most important cause of renal failure, affects approximately 30 to 40% of insulin-dependent diabetic patients [5] and is the main cause of death (30%) in these patients. Mean survival rate after the development of persistent proteinuria is about seven years [6] in the absence of any treatment. For this reason it is necessary to identify therapeutic schemes which may prevent the evolution of diabetic nephropathy. In fact each of the following treatments, that is, improvement of metabolic control [7, 8], careful control of blood pressure [9–11] as well as a low-protein intake [12, 13], was able by itself to slow the decline of renal function and to reduce the proteinuria. Thus we designed a pilot preliminary study to evaluate the long-term effect of an intensive treatment on glomerular filtration rate and albuminuria, consisting of an improvement of metabolic control, an antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitors and a low-protein diet.

Received for publication February 28, 1994
and in revised form June 20, 1994
Accepted for publication July 21, 1994

Methods

We have studied the effects of a long-term period of intensive treatment (36 months) in fourteen type I diabetic patients with impaired renal function, who were fully informed of the experimental nature of the study. Inclusion criteria were glomerular filtration rate (GFR) <70 ml · min^{-1} · 1.73 m^2 and persistent albumin excretion rate (AER) >30 μg/min. Strict metabolic control was achieved through multiple (that is, 3 to 4 daily) insulin injections; the dosage was adjusted according to glucose self-monitoring (4 times daily). The long-term intensive treatment also included antihypertensive therapy with the ACE inhibitors enalapril (10 to 20 mg/day) or captopril (25 to 50 mg/day) and a low-protein diet containing 32 ± 9 Kcal day/kg with 0.8 g/kg body wt/day of protein, of which 30% were vegetable proteins.

The clinical characteristics of the subjects are given in Table 1. None of the participants was affected by other renal or systemic disease or took any drug during the study. One of these patients experienced one episode of myocardial ischemia at the end of the second year of treatment.

Urea excretion was used to calculate protein intake from the nitrogen content of the urea and an estimated value of non-urea nitrogen of 31 mg · kg^{-1} · day [14]. Assuming a constant nitrogen balance, nitrogen intake = nitrogen content of urinary urea plus non-urea nitrogen, and protein intake (g/day) = nitrogen intake · 6.25 [15].

The adhesion to the diet was assessed by analysis of three-day weighed food records collected every six months. GFR was determined as already described [16]. To evaluate GFR a single intravenous bolus injection of ^{51}CrEDTA 1 μCu/kg (Sorin, Saluggia, Italy) was calibrated and made up to 10 ml with NaCl (0.9%), which was then administered 90 minutes after breakfast. Blood plasma samples were taken at 5, 10, 20, 30, 44, 50, 60, 80, 120, 180, 240 and 360 minutes after the injection. The results were standardized for 1.73 m^2 body surface area, using the patients surface area at the start of the study. On the day of the test the patients received their usual insulin doses; their glycemic levels were checked every hour during the test and additional insulin units were administered if glucose levels were found to be higher than 160 mg/dl. During the test the patients were in the supine

Table 1. Clinical characteristics of 14 patients with diabetic nephropathy

Age *years*	45 ± 9.5
Duration of diabetes *years*	23.5 ± 7.3
Sex	8 M/6 F
BMI *kg/1.73 m²*	25 ± 1.4
W/H ratio	0.8 ± 0.1
Insulin doses	41.3 ± 8.7
BUN *mg/dl*	19.6 ± 4
Creatinine *mg/dl*	1.08 ± 0.22
Creatinine clearance *ml/min*	61 ± 12
SBP *mm Hg*	144 ± 26
DBP *mm Hg*	89 ± 9

Abbreviations are: BMI, body mass index; W/H, waist/hip; SBP, systolic blood pressure; DBP, diastolic blood pressure.

position and were asked to avoid smoking. GFR was measured as the clearance of the isotopes under the assumption that all the tracer is excreted and that the only route of excretion is renal. Thus the total amount of tracer excreted will be equal to the quantity injected. Measurement techniques for plasma clearance may be classified as follows:

(1) Double exponential analysis utilizes all blood samples to obtain the two slopes λ and λ2.
(2) Monoexponential analysis utilizes only later plasma samples taken at 80, 120, 180, 240 and 360 minutes.
(3) The method from value distribution measurement utilizes only the sample taken at 180 minutes.

We preferred to use double exponential analysis because it is very reliable. In our laboratory the values of GFR in normal subjects range from 80 to 130 ml · min^{-1} · 1.73 m^2. The accuracy of this method, which is commonly used as a reliable technique to assess renal function is demonstrated by a correlation index with renal insulin clearance of 97%. Blood urea nitrogen was determined by Berthelot reaction, serum and urinary creatinine were measured by a modification of the Jaffé method with alkaline nitrate [17], and glycated hemoglobin (HbA_1c) by the HPLC method. AER was evaluated in three overnight urine collections by radioimmunoassay (Albumin DA, Tecnogenetics, Italy). Systolic and diastolic blood pressure were evaluated twice with a Random-Zero mercury sphygmomanometer by the same observer. During the treatment period systolic and diastolic blood pressure and body weight were monitored every month, HbA_1c levels every two months and AER every six months. GFR and creatinine clearance were measured every year.

Statistical analysis

Data are expressed as the mean ± SEM except for AER which is shown as median and range values. Paired *t*-test was used to compare the differences before and at the end of the study. All calculations were made using Statview 512 (Apple Computer Inc.). Differences were considered significant at $P < 0.05$ (two tailed).

Results

One patient ($N = 14$) showed no compliance to the treatment protocol, namely low-protein diet and antihypertensive therapy. In this patient we observed a progressive decrease in renal function with a dramatic reduction in GFR (from 70 ml/min^{-1}/1.73 m^2 to 40 ml/min^{-1}/1.73 m^2) and an increase in AER (from 1 g/liter to 5 g/liter) despite the improvement of the HbA_1c value (from 9.2% to 6.7%).

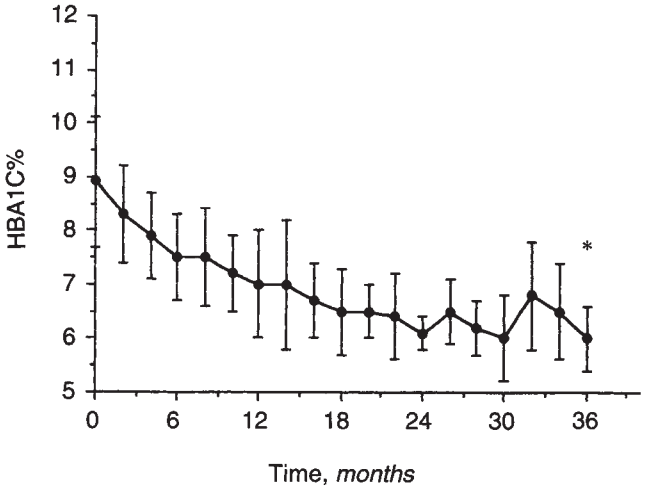

Fig. 1. *Mean HbA_1c values before and during 36 months of intensive treatment (*P < 0.0002).*

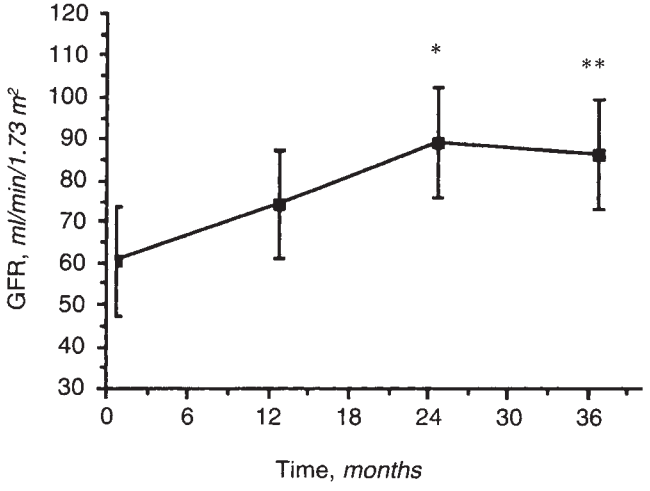

Fig. 2. *Average course of glomerular filtration rate (GFR) before and during the intensive treatment. *P < 0.0005; **P < 0.0008).*

In the other 13 patients the HbA_1c mean value was significantly lowered from 8.7 ± 0.8% to 6.5 ± 0.5% ($P < 0.0002$; Fig. 1) after three years of intensive treatment. A significant improvement of GFR was observed in these patients: 58 ± 12 ml/min^{-1}/1.73 m^2 at the beginning of the study, 72 ± 24 ml/min^{-1}/1.73 m^2 after one year, 87 ± 15 ml/min^{-1}/1.73 m^2 after two years ($P < 0.0005$) and 84 ± 11 after three years of treatment ($P < 0.0008$) (Fig. 2). Figure 3 shows GFR values for each patient during the study period. Creatinine clearance was unchanged after this period: 61 ± 12 ml/min versus 65 ± 14 ml/min (P = NS). AER decreased from 208 μg/min (range 73 to 500) to 91.3 μg/min (range 36 to 300) after one year of treatment, to 60 μg/min (range 15 to 136) after two years and to 63.8 μg/min (range 15 to 180) at the end of the study ($P < 0.05$; Fig. 4). Four patients, with macroalbuminuria, had only microalbuminuria at the end of the study.

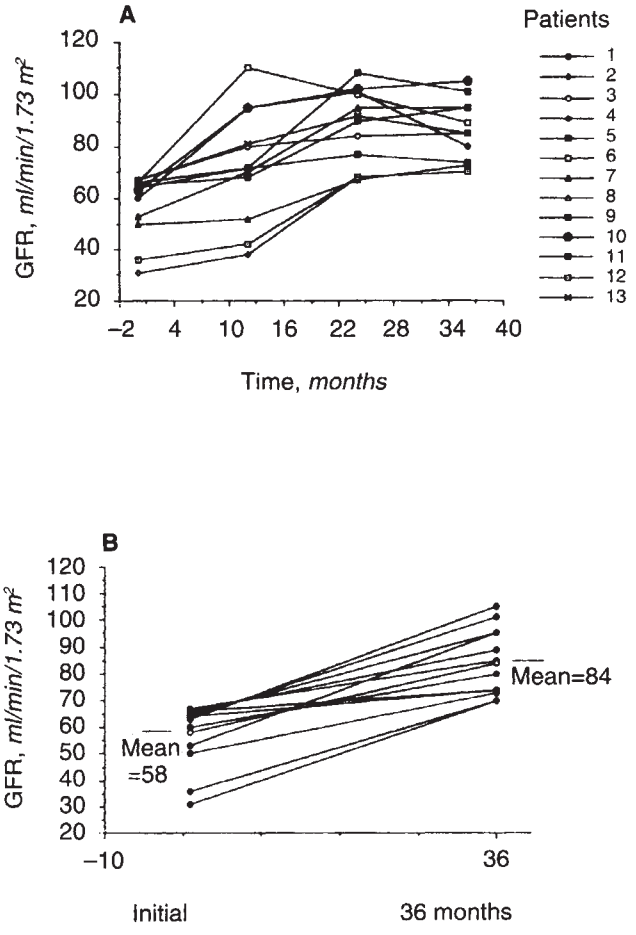

Fig. 3. A. *GFR in 13 patients before and during the intensive treatment.* **B.** Means of GFR in the same patients at the start and at the end of the study.

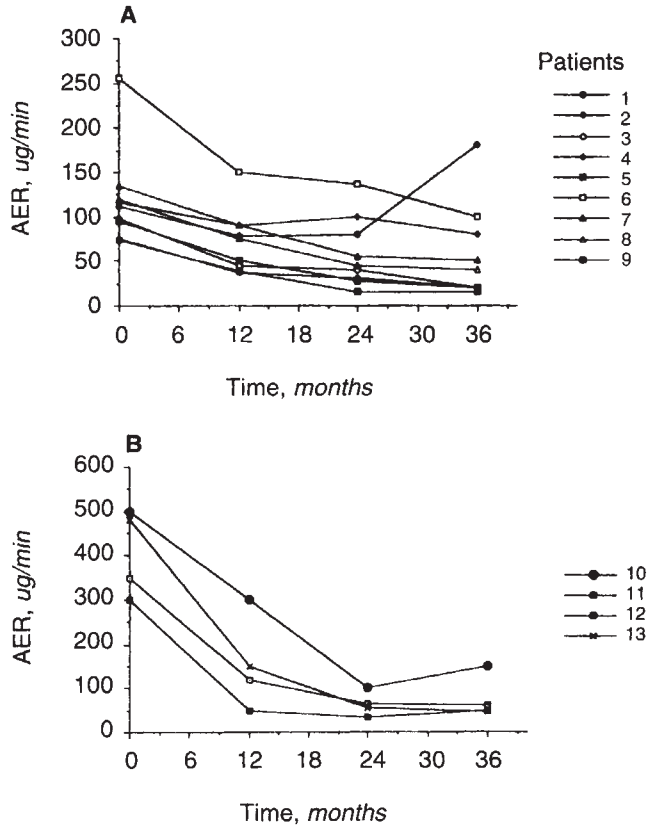

Fig. 4. *Albumin excretion rate (AER) in microalbuminuric* (**A**) *and macroalbuminuric* (**B**) *patients before and during the intensive treatment.*

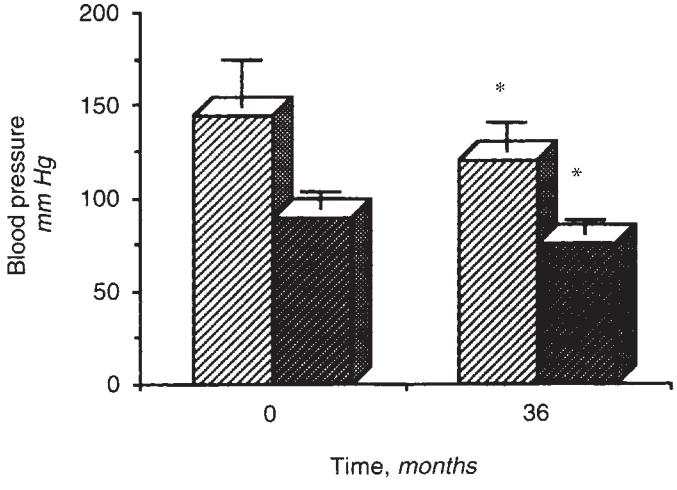

Fig. 5. *Mean blood systolic (SBP,* ▨*) and diastolic pressure (DBP,*) *before and after two years of antihypertensive treatment (*P < 0.01).*

ACE-inhibitor treatment resulted in a reduction of systolic (144 ± 26 mm Hg vs. 120 ± 15 mm Hg) and diastolic blood pressure (89 ± 9 mm Hg vs. 75 ± 8 mm Hg; $P < 0.01$; Fig. 5). No change was observed in blood urea nitrogen and creatinine plasma levels during the period of intensive treatment.

The effect of the same treatment protocol is currently being studied in three additional patients: preliminary results show that after a one year follow-up GFR improved from 67 ± 12 ml/min^{-1}/1.73 m^2 to 109 ± 15 ml/min^{-1}/1.73 m^2; AER reduced from 90 μg/min to 41.6 μg/min, and HbA_1c is significantly lowered from 7.7 ± 0.3% to 6.8 ± 0.5%.

Discussion

The aim of our study has been to evaluate the effect of three associated treatments (anti-hypertensive therapy, low-protein diet, multiple insulin injections) on the progression of diabetic nephropathy. Because each one of these treatments has been shown to reduce microalbuminuria and progressive GFR decline we deemed it not ethical to have a control group without any treatment.

Previous studies have shown that each type of intervention *per se* is able to reduce albumin excretion rate and the rate of monthly decline of renal function.

Several studies found a decreased impairment of GFR and a reduction in urinary albumin excretion in diabetic patients with nephropathy treated with a low-protein diet (0.6 g/kg) [12, 13]. In our study the reduction of the daily protein intake from 1.35 g/kg to 0.80 g/kg was attained through an increase in the amounts of bread, pasta, legumes and fruit, and a reduction

of the amounts of cheese, meat and fish. This modification decreased the quantity of animal proteins and was quite compatible with Italian nutritional habits; this made compliance to the diet easier for the patients. A low protein intake protected against the progressive sclerosis of functioning glomeruli in experimental diabetic nephropathy [18, 19]; however, the relevance of these animal studies to human renal disease is unknown. On the other hand, dietary protein is known to exert profound effects on the renin-angiotensin-aldosteron system. In fact, a low-protein diet *per se* suppresses this system [20, 21], ameliorating renal function. We didn't find any significant change of serum creatinine and creatinine clearance after three years. These parameters are unreliable indicators of kidney function in renal disease. When patients are on a low-protein diet, there is a variation in the creatinine pool and metabolism which is independent from the changes in GFR [12]. Furthermore, the measurements of creatinine clearance can overestimate GFR in patients with severe renal insufficiency, while variability in urine collections may result in poor reproducibility of these measurements [22].

Other studies have evaluated the effect of long-term antihypertensive treatments on the progression of diabetic nephropathy [9, 23, 24]. Many authors have performed different studies comparing ACE inhibitors with β-blockers or with calcium antagonists [10, 25–29] and all of these studies have shown that early antihypertensive treatment *per se* was able to slow the decline of renal function in diabetic nephropathy and dramatically improve the survival rates [30, 31]. ACE inhibitor therapy also has an antiproteinuric effect independent from the effect on systemic blood pressure [32–34]; this may be due either to diminished glomerular capillary idraulic pressure or to enhanced intrinsic selectivity of the glomerular barrier wall. In fact antihypertensive treatment with ACE inhibitors is able to improve both size and charge selective properties of glomerular capillary filtration barrier [35]. There is a strong correlation between level of microalbuminuria and rate of decline in GFR [36]. It has been demonstrated that a pronounced decrease in proteinuria after the start of antihypertensive treatment predicts a more benign course of renal disease in IDDM patients [23, 24]. Other mechanisms proposed to explain the improvement of renal function induced by ACE inhibitors are: (1) a block of mesangial cell growth [37] through the inhibition of the production of angiotensin II, which is a growth factor; and (2) the inactivation of kininase II, a kinin degrading enzyme, resulting in accumulation of bradykinin in the renal circulation [38, 39].

In agreement with the above-mentioned reports our results show that treatment with ACE inhibitors induced a decrease of albumin excretion rate and a regression from macroalbuminuria to microalbuminuria in four of the patients. Furthermore, the activity of angiotensin converting enzyme which was elevated in our patients before the treatment was completely suppressed by ACE inhibitors (data not shown).

The effect of metabolic control on the development and progression of diabetic nephropathy in type 1 (insulin-dependent) diabetic patients has been widely studied with conflicting results: in the Oslo study [40] and in the Steno study [7, 41] the reduction of GFR was shown to be slower in patients with early nephropathy treated with CSII than in those treated with conventional therapy. The DCCT [42] has shown that in the intensive therapy group the risk of albuminuria was reduced by 56% and that very few patients developed nephropathy. Recently it has been shown that the improvement of blood glucose control retards the development of structural changes in early diabetic nephropathy [43]. In patients with diabetic nephropathy Nyberg, Blohmè and Norden [44] found a significant correlation between HbA_1c levels and rate of decline in GFR, while other studies [3, 45] found no relationship between the two parameters. On the other hand, Viberti et al [46] showed that the progression of diabetic nephropathy was not reversed by the improvement of glycemic control. In our study good metabolic control, obtained with multiple insulin injections, improved renal function only in association with a low-protein diet and antihypertensive treatment. In fact we observed that the only patient who showed no compliance to diet and to antihypertensive therapy had a progressive decline in GFR in spite of good metabolic control.

The pathogenesis of diabetic nephropathy is not fully understood and a variety of mechanisms have been hypothesized (genetic predisposition, hyperglycemia *per se,* non-enzymatic glycosilation, hyperfiltration). Thus it is possible that a multiple therapeutic intervention, such as the one employed in our study, can act on the different pathogenetic mechanisms to delay or to change the natural evolution of diabetic nephropathy.

In conclusion, we suggest that a combination of low-protein diet, antihypertensive treatment and good metabolic control in patients with early alterations of renal function (proteinuria and reduction of GFR) can postpone the progression to renal failure. A longer follow-up is mandatory to verify if this treatment is able to preserve the kidney from renal failure.

Acknowledgments

This study was supported by a grant from the Catholic University. The authors thank the patients for participating in this study, the staff of the Diabetic Outpatients Clinic, and Giovanni D'Errico, M.D. for his assistance. This work was presented in abstract form at 53rd American Diabetes Association meeting in Las Vegas in June 1993.

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