THE OUTCOME OF ADVANCED CHRONIC NEPHROPATHY IN TYPE 1 AND TYPE 2 DIABETIC AND NON-DIABETIC PATIENTS: A PROSPECTIVE STUDY

J.-J. ALTMAN, N. ELIAN, S. GRUN, H.-G. GERARD, S. FELDMAN

SUMMARY - To compare end-stage progression of nephropathy in type 1 and type 2 diabetic patients and non-diabetic subjects, we prospectively studied 92 patients with advanced uraemia not yet on dialysis (mean age 57.2 ± 15.0 years), with a serum creatinine level above 200 µmol/L. The study included monthly serum creatinine (SC) measurements and quarterly outpatient follow-up (mean 10.8 ± 7.1 months, range 1-21). Sixty subjects (65.2 %) were diabetic (28 type 1 and 32 type 2). At inclusion, 95.6 % of patients had anti-hypertensive medications. Drug category, dosage and combination were similar for both groups. Blood pressure (≤ 130/85 mmHg) and glucose level targets (fasting ≤ 7.5 mmol/L and postprandial ≤ 10 mmol/L) were obtained in all patients. Initial SC was not significantly different between diabetic and non-diabetic patients (426.5 ± 189.4 µmol/L vs. 405.1 ± 201.9 µmol/L). SC increased significantly faster in diabetic than non-diabetic patients (respectively 3.9 ± 6.1 % and 1.5 ± 4.6 % monthly, p < 0.05), with no difference between type 1 and type 2 diabetes. One-third (33.7 %) of all patients started dialysis during follow-up (40 % diabetic and 22 % non-diabetic). Their weight, Body mass index, age, sex ratio, treatment and aetiology were similar. During follow-up, the patients (29.4 %) who sustained a major vascular event differed only in age (62.1 years vs. 55.2 years; p < 0.001). In this study, diabetic renal disease worsened significantly faster than other nephropathies, in spite of proper normalisation of blood pressure and glucose level. Therefore, it is essential to diagnose and manage Type 2 diabetes early to avoid encumbering dialysis centres with older patients.

Key-words: diabetes, nephropathy, dialysis, vascular disease, arterio-venous fistula.

RÉSUMÉ - Devenir de la néphropathie chronique avancée chez des sujets diabétiques de type 1 et de type 2 et des patients non-diabétiques: étude prospective.

Pour comparer la progression vers l’insuffisance rénale terminale des néphropathies des diabétiques de type 1 et de type 2 de celle des non-diabétiques, nous avons de façon prospective étudié 92 patients en insuffisance rénale avancée avant dialyse (âge moyen 57.2 ± 15.0 ans), dont le taux de créatinine sérique était supérieur à 200 µmol/L. La créatinine sérique (SC) a été mesurée chaque mois, et le suivi ambulatoire assuré tous les 4 mois (moy 10.8 ± 7.1 mois, de 1 à 21). Soixante sujets (65.2 %) étaient diabétiques (28 type 1 et 32 type 2). À l’inclusion, 95.6 % des patients étaient sous anti-hypertenseurs, le type de médication, les doses et associations thérapeutiques non différentes entre groupes. Les objectif de pression artérielle (≤ 130/85 mmHg) et de glycémie (à jeun ≤ 7.5 mmol/L et postprandial ≤ 10 mmol/L) ont été atteints chez tous les patients. La valeur initiale de SC n’était pas différente (426.5 ± 189.4 µmol/L diabétiques vs. 405.1 ± 201.9 µmol/L non-diabétiques). La valeur de SC s’est élevée plus rapidement chez les diabétiques (respectivement 3.9 ± 6.1 % vs 1.5 ± 4.6 %/mois, p < 0.05), sans différence entre groupes. Un tiers (33.7 %) des patients entra en dialyse durant le suivi (40 % diabétiques and 22 % non-diabétiques). Leur poids, indice de masse corporelle, âge, sexe ratio, traitement et étiole ne différaient pas. Durant le suivi les patients qui ont présenté un événement cardio-vasculaire majeur (29.4 %) différaient par l’âge (62.1 ans vs 55.2 ans ; p < 0.001). Dans cette étude, l’atteinte rénale des diabétiques s’est aggravée plus rapidement que celle des néphropathies non-diabétiques, malgré l’excellent contrôle tensionel et glycémique. Il convient donc de dépister et de traiter les néphropathies diabétiques de type 2 en particulier pour tenter de réduire l’encombrement des centres de dialyse par ces patients.

Mots-clés : diabète, néphropathie, dialyse, maladies cardio-vasculaires, fistule artério-veineuse.
Diabetic nephropathy is one of the most common causes of end-stage renal failure in the Western world [1]. The effect of intensive treatment of diabetes on the progression of long-term renal complications [2] and its epidemiological approach [3, 4] have been established for Type 1 diabetes. However, discrepancies between Type 1 and Type 2 diabetes have only been documented in early stages of diabetic nephropathy. We prospectively studied subjects with advanced uraemia not yet on dialysis to compare end-stage progression of nephropathy in Type 1 and Type 2 diabetic patients and non-diabetic patients under optimal blood pressure control and in diabetic patients under optimal normoglycaemic control.

### PATIENTS AND METHODS

The study was carried out in a specialised nephro-diabetology centre, which is a referral unit for advanced diabetic nephropathy in Paris. All consecutive nephropathic patients with a serum creatinine level ≥200 µmol/L, were included during a 15-month period. There were no exclusion criteria.

The 92 patients (59 male, 33 female) were classified into three groups according to the underlying nephropathic aetiology. Sixty patients (65.2 %) were diabetic (28 insulin-dependent and 32 non-insulin-dependent). The remaining 32 patients were not diabetic. The classification of the 60 diabetic patients complied with National Diabetes Data Group criteria. Their duration of diabetes was at least 15 years, and they showed no clinical or biological evidence of non-diabetic nephropathy. The 32 non-diabetic patients had polycystic kidney disease, nephroangiosclerosis or chronic interstitial nephropathy. The Quetelet index [weight (kg)/square height (m²)] was used to calculate body mass index (BMI). Blood pressure was measured with a standard mercury sphygmomanometer after a 10-min rest in supine position. Diastolic pressure was recorded at the disappearance of Korotkoff’s sound (phase 5). The category, combination and dosage of anti-hypertensive drugs were noted. Anti-hypertensive therapy aimed for blood pressure values of 130/85 mmHg. Maintenance of optimal supine blood pressure control and in diabetic patients under optimal blood pressure control and in diabetic patients under optimal normoglycaemic control.

### RESULTS

**Clinical and biological characteristics** – The overall mean age of subjects was 57.2 ± 15.0 years, and the mean BMI was 25.2 ± 4.2 kg/m², with no difference between males and females. The mean initial SC was 419.1 ± 193.0 µmol/L (range: 203-998 µmol/L) and was significantly higher in males than in females (449.4 ± 200.6 µmol/L vs. 364.8 ± 161.7 µmol/L, p = 0.03), whereas the creatinine clearance rate was not different. Clinical and biological parameters in relation to aetiology are shown in Table I. Type 1 diabetic patients were significantly younger (p < 0.001) and leaner (p < 0.001) than Type 2. The mean initial SC was similar in the 3 groups. Mean dietary protein intake was also similar in all patients. Target fasting and postprandial blood glucose were attained in all diabetic patients, with only occasional mild hypoglycaemic attack.

**Anti-hypertensive treatment** – At inclusion, 95.6 % of patients were receiving one or more anti-hypertensive agents. The administered medications were calcium antagonists (71.7 % of patients), diuretics (63.0 %) and cardioselective beta-blockers (48.9 %). These 3 categories were included in the most frequently prescribed 3-drug combinations (15.2 % of patients). Other prescriptions included angiotensin-converting enzyme (ACE) inhibitors (21.7 %), central anti-hypertensive drugs, vasodilators and alpha-1-receptor blockers. Each patient received an average of 2.5 different anti-hypertensive drugs. During follow-up, drug category, combination and dosage were similar for all groups, and between males and females. The dosage was adjusted whenever blood pressure exceeded 130/85 mmHg. Maintenance of optimal supine blood pressure was successful in all patients.

**Follow-up** – Mean follow-up (10.8 ± 7.1 months, range 1-21) did not differ in relation to the nephropathic aetiology. Figure 1 shows the patient actuarial survival rate. During the study, 9 (9.8 %) patients...
died: 2 Type 1, 3 Type 2 and 4 non-diabetic. Dialysis was started on joint evidence of poor cardiovascular tolerance and extreme biochemical figures. At the end of the study, 66.3% of patients were not on dialysis, despite an elevated initial SC level ($353.6 \pm 140.1 \mu\text{mol/L}$). An arteriovenous fistula was created in 45% of patients when dialysis was expected to start during the next 3 months. The interval was $7.8 \pm 6.1$ months between inclusion and dialysis and $8.1 \pm 9.2$ months between the creation of a fistula and dialysis. These periods were similar regardless of the nephropathic aetiology.

![Graph showing survival and dialysis status over time.](image)

**Fig. 1.** Actuarial follow-up of patients.

**Fig. 2.** Percentage of overall serum creatinine increase in diabetic and non-diabetic patients.
Nephropathic course – Initial SC was similar in the 3 groups, but higher at the end of the study in diabetic (520.8 ± 260.9 µmol/L) than non-diabetic patients (441.3 ± 266.4 µmol/L). The mean overall increase of SC was 3.1 ± 5.7 % monthly. SC rose significantly faster (p < 0.05) in diabetic nephropathy (3.9 ± 6.1 % monthly) than in other nephropathies (1.5 ± 4.6 % monthly), with no difference between Type 1 and Type 2 diabetes (Fig. 2). These results did not change when adjusted for age and BMI.

Dialysis: One-third (33.7 %) of patients were introduced to dialysis during follow-up. At the start of dialysis, mean SC was 785.2 ± 205.6 µmol/L. Forty percent of patients were dialysed in the diabetic group, and 22 % in the non-diabetic group (NS). Weight, age, sex ratio, BMI, blood pressure levels, ongoing treatment and aetiology were similar in dialysed and non-dialysed patients. The two predictive factors for dialysis were the initial SC level (547.9 ± 218.8 µmol/L in dialysed patients vs. 353.6 ± 140.1 µmol/L in non-dialysed patients; p < 0.001) and the monthly SC increase (8.6 ± 6.3 % vs. 0.7 ± 3.2 %; p < 0.001).

Cardiovascular events – Table II compares patients who developed vascular events during follow-up with those who did not. Major vascular events (severe arteritis, myocardial infarction or stroke) occurred in 29.4 % of patients during the study, regardless of BMI, diabetes or dialysis. These patients were significantly older than the others (p < 0.001). The category, combination and dosage of anti-hypertensive drugs, the mean initial SC level and the nephropathic course were similar. The monthly SC increase was not different between patients who experienced a vascular event and the others.

DISCUSSION

Patients were classified into type 1 and type 2 diabetes according to National Diabetes Data Group criteria. Type 1 diabetic patients were statistically younger and thinner than type 2, with diabetes duration over 20 years and onset always before the age of 30 years. Since several type 1 patients were enrolled in a kidney-transplant programme, they underwent dynamic studies of C-peptide levels, which were consistently negative. A third or more of type 2 patients are reported to developed a non-diabetic nephropathy [6]. However, no diabetic patients in our cohort showed any clinical or biological evidence of non-diabetic nephropathy. All type 2 patients had retinopathy and a long history of diabetes. Renal biopsy performed in more than 50 % of them confirmed the diabetic nephropathy.

In clinical practice, serial SC measurement is a reliable alternative to glomerular filtration rate. A satisfactory correlation also exists between the Cockroft-Gault formula and progress toward end-stage renal disease. HbA1 is not reliable in monitoring uraemic diabetic patients. HbA1c is more adequate, but many of our patients were regularly transfused. Therefore, this criterion was not taken into account.
and we relied on self-monitoring of blood glucose, which provided a very satisfactory control.

All patients had their blood pressure maintained below or equal to 130/85 mmHg, according to recent recommendations [7]. None had diastolic blood pressure below 70 mmHg.

Drug category, dosage and combination were similar for all groups. The choice of anti-hypertensive drugs and their possible effect on the rate of decline in renal function has only been documented in early stage nephropathy in type 1 diabetes [8, 9]. One report [10] concerned patients with severe nephropathy, though far less advanced than in our cohort. Drug choice was determined by the need to achieve the recommended blood pressure levels and by the presence of associated diseases. Calcium blockers were the most frequently prescribed anti-hypertensive drugs because of concurrent angina pectoris. To tighten blood pressure control, we willingly prescribed ACE inhibitors to one-fifth of patients despite a high creatinine level.

Advanced renal disease is a vascular risk factor unrelated to SC level. The relationship between hyperglycaemia and vascular accidents remains controversial. Conversely, smoking and serum cholesterol and triglyceride levels increase the occurrence of vascular accidents. This study was not designed to test these parameters. Age was the only detected predisposing factor for vascular accidents.

There were 9 deaths during follow-up: 5 diabetic and 4 non-diabetic patients. Although survival of diabetic patients on dialysis has improved considerably in recent years, the prognosis is reported to be worse than for non-diabetic patients [11-14]. We did not observe such poor outcome. Moreover, the patients who died were not all on dialysis. One possible determining factor is the vascular insult cumulated during the pre-dialysis course [12, 15].

In our prospective study, which consisted of a remarkably large cohort of very advanced renal insufficiency patients, diabetic nephropathy worsened faster than any other nephropathy, regardless of the type of anti-hypertensive treatment, age or BMI. Although type 1 and type 2 diabetic patients are reported to show differences in the course of nephropathy at early stages of the disease [16], this was not seen in our cohort of advanced nephropathy. In the 1970s, diabetic nephropathy was considered to be a rapidly progressive disease [17]. However, data collected during the 1980s [8, 9, 18] indicated that it was possible to slow or even halt the progression of early stages in type 1 patients, mainly by adequate control of blood pressure and glycaemia. Previous reports on blood glucose [19-21] or blood pressure normalisation [21, 22] also suggested that the course of advanced nephropathy in diabetic and non-diabetic patients could be slowed. In our study, it was not possible to prevent the worsening of kidney function in very advanced diabetic nephropathy in spite of optimal control of blood pressure and glycaemia.

During follow-up, there was no difference in the occurrence of dialysis between diabetic and non-diabetic patients. If follow-up was extended, diabetic patients would have shown a higher incidence of dialysis than non-diabetic patients because of the rapid rise of their SC level.

## CONCLUSION

We studied a unique cohort with very advanced diabetic nephropathy in which the course of chronic renal failure was not halted, regardless of the nephropathic aetiology. Nevertheless, two-thirds of patients were not dialysed at the end of the study, even though the mean initial creatinine level was above 400 µmol/L. Furthermore, the mean interval before dialysis was around 8 months. In spite of diligent efforts to achieve blood pressure and glycaemia control, the deterioration rate remained high in diabetic patients, in contrast to reports on early diabetic nephropathy.

Renal insufficiency in type 2 diabetes, particularly in elderly patients, is now the leading cause of expensive replacement therapy [23]. Every effort should be made to ensure early diagnosis and management of the underlying disorder to prevent the invasion of dialysis centres by older type 2 patients [24, 25]. Hopefully, genetic studies will eventually identify patients at risk of end-stage nephropathy.

This work was supported in part by Lilly-France, 92213 Saint-Cloud, France.

**REFERENCES**


