Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria

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Abstract

Background. Intervention studies in microalbuminuric type 2 diabetic patients have demonstrated that it is possible to avoid progression to overt diabetic nephropathy and even to achieve regression to normoalbuminuria. However, the long-term impact of stabilization/regression in albuminuria on decline in glomerular filtration rate (GFR) has not been established.

Methods. 151 patients with type 2 diabetes and microalbuminuria at baseline in whom GFR was measured at least three times during 7.8 years of follow-up were divided into three groups according to the level of albuminuria during follow-up. Overt nephropathy was diagnosed as a urinary albumin excretion rate (AER) > 300 mg/24 h and remission to normoalbuminuria was defined as an AER < 30 mg/24 h at the last examination.

Results. During follow-up, 46 patients achieved remission to normoalbuminuria, 58 remained microalbuminuric and 47 patients progressed to overt nephropathy. The mean (± SE) yearly decline in GFR was lowest (2.3 ± 0.4 ml/min/year) in patients who obtained remission, in comparison with patients remaining microalbuminuric, in whom the decline was 3.7 ± 0.4 ml/min/year, and patients progressing to overt nephropathy, who had a decline in GFR of 5.4 ± 0.5 ml/min/year (ANOVA, \(P < 0.001\)). Start of antihypertensive treatment during follow-up was strongly associated with remission to normoalbuminuria [odds ratio: 2.32; 95% confidence interval (CI): 1.09–4.93] whereas a decrease in HbA\textsubscript{1c} by 1% increased the probability for remission (odds ratio: 1.48; 95% CI: 1.11–1.97).

Conclusions. Remission to normoalbuminuria was associated with a decreased GFR decline during 7.8 years of follow-up in type 2 diabetic patients with microalbuminuria. Antihypertensive therapy and improved glycaemic control were independent predictors for remission.

Keywords: glomerular filtration rate; kidney function; remission; risk reduction; type 2 diabetes mellitus; urinary albumin excretion rate

Introduction

Each year, 4–9% of type 2 diabetic patients with persistent microalbuminuria develop diabetic nephropathy [1–7]. Intervention studies have demonstrated that it is possible to avoid progression to overt diabetic nephropathy and even to achieve regression to normoalbuminuria [6,8–10]. In type 1 diabetes and in non-diabetic nephropathy, reduction of albuminuria after initiation of antihypertensive treatment is a good predictor of the long-term rate of decline in kidney function [11,12]. However, the impact of the regression/progression of the urinary albumin excretion rate (AER) on glomerular filtration rate (GFR) decline has been difficult to establish due to the small number of patients and rather short duration of most studies. Furthermore, the long-term course of GFR in type 2 diabetic patients with microalbuminuria remains to be investigated.

Based on data from the Steno-2 Study carried out for 7.8 years in 160 type 2 diabetic patients with persistent microalbuminuria at baseline [13], we aimed at evaluating the rate of decline in GFR according to normo-, micro- and macroalbuminuria. A secondary aim was to identify regression/progression promoters for the decline in GFR in these patients.

Subjects and methods

Patients

The study design and main results of the Steno-2 Study have been reported in detail elsewhere [4,13]. In brief, 160 microalbuminuric type 2 diabetic patients were randomized to conventional (\(n = 80\)) or intensified multifactorial treat-
men targeting several concomitant risk factors. Patients in the intensive therapy group were treated with a stepwise introduction of lifestyle and pharmacological interventions intended to maintain glycosylated haemoglobin (Hb) values below 6.5%, blood pressure below 130/80 mmHg, fasting serum total cholesterol levels below 4.5 mmol/l and fasting serum triglyceride levels below 1.7 mmol/l. Recommended lifestyle interventions included reduced intake of dietary fat, regular participation in light or moderate exercise and cessation of smoking. All participants in the intensive therapy group were also advised to take aspirin and an angiotensin-converting enzyme inhibitor (or, if contraindicated, an angiotensin II-receptor antagonist), regardless of blood pressure. Mean follow-up was 7.8 years. Throughout the study period the intensive group had significantly lower values of HbA1C, fasting serum levels of total cholesterol, low-density lipoprotein-cholesterol and triglycerides, systolic and diastolic blood pressure and urinary AER. These changes were associated with significant reductions in the risk for macrovascular as well as microvascular disease (relative risk reduction was 53% for cardiovascular disease, 61% for progression to nephropathy, 58% for progression in retinopathy and 63% for progression in autonomic neuropathy) [13]. Kidney function was evaluated at baseline and after 2, 4 and 8 years. All patients included in the Steno-2 Study were eligible for the present analysis. The 151 patients in whom GFR was measured at least three times during follow-up were included. Patients were divided into three groups according to the level of albuminuria during follow-up. Overt nephropathy was diagnosed as a urinary AER >300 mg/24 h in at least two of three consecutive 24h sterile urine collections during follow-up. Remission to normoalbuminuria was defined as a urinary AER <30 mg/24 h in at least two of three consecutive 24 h sterile urine collections at the 8 year examination. Remaining patients were classified in the microalbuminuric group.

The protocol was in accordance with the Helsinki Declaration and was approved by the local ethical committee. All patients gave written informed consent.

**Procedures**

All investigations were performed after an overnight fast. Patients were advised not to take their morning medication on the day of examination. GFR was measured after a single intravenous injection of 3.7 MBq 51Cr-EDTA by determination of the radioactivity in venous blood samples taken 180, 200, 220 and 240 min after the injection [14]. Results were standardized for 1.73 m2 body surface with the body surface at the start of the study used throughout the study. Albuminuria was measured with an enzyme-linked immunoosorbent assay technique in three consecutive 24 h urine samples collected immediately before the day of examination [15]. HbA1C was measured by ion-exchange high-performance liquid chromatography (Bio-Rad VARIANT, Hercules, CA, USA) and the non-diabetic reference range in our laboratory was 4.1–6.4%. Serum levels of total cholesterol and creatinine were measured by routine methods. Blood pressure was measured twice in both arms with a Hawksley random zero sphygmomanometer in the supine position after 20 min rest and averaged. Information about smoking status was derived from interviews. Patients smoking one or more cigarettes per day were classified as smokers.

**Statistics**

Unless otherwise noted, results are given as means±SE. Linear regression analysis (least squares method) was used to determine the slope of GFR for each patient. Analysis of variance and Student’s t-tests were used to compare baseline variables and the decline in GFR between the three groups according to the level of albuminuria. In case of non-normally distributed variables, the Kruskal–Wallis test was used. The χ2 test was used to compare frequencies. Logistic regression analysis was used to identify independent predictors for remission to normoalbuminuria or progression to overt nephropathy, respectively. Analysis of covariance was used to compare changes in GFR between groups adjusting for differences in baseline variables and their interaction terms, including the interaction term between original treatment allocation and urinary AER as a continuous variable. All analyses have been adjusted for original treatment allocation.

All calculations were performed with a commercially available program, SPSS 11.0 (SPSS, Chicago, IL, USA).

**Results**

Median follow-up time was 7.8 years (range: 3.0–8.8 years). During follow-up, 46 patients achieved remission to normoalbuminuria, 58 remained microalbuminuric and 47 progressed to overt nephropathy. Baseline characteristics for these three groups are seen in Table 1. At baseline the groups differed significantly in age, urinary albumin excretion, diastolic blood pressure and in the number of patients from the two original treatment groups.

The three groups differed significantly in the rate of decline of glomerular filtration (P<0.001). The mean ± SE annual decline in GFR for patients who obtained remission was 2.3±0.4 ml/min/year, for patients remaining microalbuminuric the decline was 3.7±0.4 ml/min/year and, finally, the decline was 5.4±0.5 ml/min/year for patients progressing to overt nephropathy (Figure 1). Analysing each of the two original treatment groups separately, the same trend was seen in the intensive therapy group (P=0.002) and in the conventional therapy group (P=0.006). Adjusting for significant differences between groups at baseline (Table 1), the only significant predictors for the rate of decline in GFR was the level of albuminuria (normoalbuminuria, microalbuminuria or overt nephropathy) (P=0.003) and increasing age (P=0.003).

Because of heterogeneity of albuminuria in type 2 diabetes, patients with known diabetic retinopathy at baseline (n=41) were analysed separately. The annual decline of GFR was 3.1±0.7, 4.2±0.8 and 5.8±0.7 ml/min/year for patients obtaining remission, remaining microalbuminuric or progressing to overt nephropathy, respectively (P=0.008).
The impact of urinary AER as a continuous variable for the decline in GFR was examined for the combined cohort. A decrease in the geometric mean of urinary AER during follow-up was significantly associated with a decreased decline in GFR ($P = 0.002$). As in the categorical analysis, age was also an independent predictor ($P = 0.001$), which was also the case when baseline urinary AER was applied as a continuous variable ($P = 0.03$).

As shown in Table 2, the level of urinary AER was an independent baseline predictor for both remission and progression during follow-up. Furthermore, the presence of retinopathy at baseline significantly increased the risk for progression to overt nephropathy. Similarly, an increase in HbA1c during follow-up was associated with an odds ratio of 1.43 [95% confidence interval (CI): 1.08–1.88] for the progression from microalbuminuria to overt nephropathy.

During follow-up, 53 patients started antihypertensive treatment and of these 47 (89%) were given drugs blocking the renin–angiotensin system (RAS). Start of antihypertensive treatment during follow-up was strongly associated with remission to normoalbuminuria (odds ratio: 2.32; 95% CI: 1.09–4.93).

Initiation of specific treatment with RAS-blockade during follow-up ($n = 67$), including patients who were already treated with other forms of antihypertensive drugs at baseline ($n = 14$), was also associated with a diminished risk for progression to overt nephropathy (Table 2). Gender, age, known duration of diabetes, glycaemic control, fasting serum level of total cholesterol level and smoking habits at baseline were not significant predictors for a change in the level of albuminuria during follow-up. Similarly, changes in blood pressure, fasting serum lipid values, weight and smoking habits during follow-up did not independently predict the outcome of the level of albuminuria.

**Discussion**

Our prospective study for a period of 7.8 years in 151 patients with type 2 diabetes and persistent microalbuminuria demonstrates that the rate of decline in GFR is closely related to the presence of persistent normo-, micro- or macroalbuminuria during follow-up, even after adjustment for traditional progression promoters. Remission to normoalbuminuria was achieved in 30% of patients and was associated with a significant reduction in the rate of GFR decline. Progression to overt nephropathy was demonstrated in 31% of patients and this event was associated with significant worsening of kidney function.
Although studies have demonstrated that intervention in type 2 diabetic patients with microalbuminuria can retard progression in or reduce AER, the rate of remission to normoalbuminuria is only reported in a few studies [6,8–10]. In a study comparing the treatment effect of enalapril with that of nifedipine on urinary AER during a 5.5 year follow-up period in hypertensive type 2 diabetic patients, fewer enalapril-treated microalbuminuric patients progressed to macroalbuminuria and significantly more patients reverted to normoalbuminuria (24% with enalapril compared with 15% with nifedipine) [8]. Similarly, 29% of hypertensive microalbuminuric type 2 diabetic patients treated with irbesartan 150 or 300 mg for 2 years obtained remission to normoalbuminuria compared with 21% treated with placebo in the IRMA-2 trial [6]. For the same level of obtained blood pressure and blood pressure reductions, another angiotensin II-receptor antagonist, valsartan, also proved more effective than the calcium-channel blocker amlodipine in reducing urinary AER in type 2 diabetic patients with microalbuminuria, including the subgroup with baseline normotension. Overall, 30% of patients treated with valsartan for 24 weeks obtained remission to normoalbuminuria [10].

In accordance with these studies [6,8–10], the initiation of antihypertensive treatment and, especially, RAS blockade during follow-up in our study was proportionally correlated with regression to normoalbuminuria and inversely correlated with progression to overt nephropathy. It is notable that this also applies for initiation of blockade of the RAS in patients already treated with other antihypertensive drugs.

Intensive treatment of hyperglycaemia significantly reduced the progression rate to macroalbuminuria from 36% to 12% among microalbuminuric type 2 diabetic men randomized to intensive compared with standard glucose-lowering treatment during 2 years, yet no significant difference was seen between groups in the number of patients obtaining normoalbuminuria (29% vs 36%) [9].

Smoking was not a risk factor for progression to overt nephropathy in the present study. In contrast, a recent retrospective study in 273 Italian type 2 diabetic patients followed for 3.5 years identified smoking as the strongest predictor for progression to nephropathy [16] and current smoking was also found to be a significant risk factor for progression to end-stage renal disease (ESRD) requiring dialysis in Japanese type 2 diabetic patients during a follow-up of 5.6 years [17]. However, earlier cross-sectional studies have not identified smoking as a risk factor for nephropathy [18–20]. Similarly, during 20 years of follow-up in the Rochester study, smoking was not found to be a risk factor for persistent proteinuria [21]. Recently, in a prospective follow-up study of 311 type 1 diabetic patients with overt diabetic nephropathy, smoking was not an independent predictor for progression in diabetic kidney disease [22]. It is important to notice that bias may be present due to selective mortality.

The level of urinary AER is merely a surrogate marker for the decline in kidney function and, eventually, ESRD. However, the diminution of proteinuria indicates protection from ongoing kidney damage and would probably translate into preservation of GFR in the longer term. In studies of type 2 diabetic patients with microalbuminuria, the average rate of decline of GFR varies considerably, ranging from 0 to 3.4 ml/min/year [2,5,13]. In Pima Indians, GFR remained stable during a 4 year observational study in patients with normo- as well as microalbuminuria compared with a significant decline of 10.9 ml/min/year in patients with macroalbuminuria, suggesting that as long as AER is in the microalbuminuric range kidney function is not threatened [5]. Also, a rather small decline of 1 ml/min/year was found in Indian normotensive type 2 diabetic patients with persistent microalbuminuria treated with placebo or an angiotensin-converting enzyme inhibitor during a 5 year period [2]. Recent data from the IRMA-2 trial also found a slow sustained (3–24 months) rate of decline in creatinine clearance of 1.2–2.4 ml/min/year with no significant differences between the placebo- and the irbesartan-treated groups [6].

In the Steno-2 Study, intensified multifactorial intervention reduced the relative risk of progression to overt nephropathy by 61% as compared with conventional treatment, yet the rate of decline in GFR during an average follow-up of 7.8 years was similar in the two groups [13]. The present analysis revealed that the relatively high average yearly decline in GFR of 3.8 ml/min/year in the entire cohort of the Steno-2 Study is ascribed to a high rate of decline in kidney function in patients progressing to macroalbuminuria,
an intermediate decline in patients pertaining microalbuminuria and a rather slow deterioration of kidney function in microalbuminuric type 2 diabetic patients obtaining remission.

Patients enrolled in the Steno-2 Study did not have kidney biopsies performed, thereby, leaving the possibility that patients achieving remission during follow-up did, in fact, not have diabetic kidney disease. Kidney biopsy studies have demonstrated the presence of various histological patterns in patients with type 2 diabetes and that deterioration in GFR is associated with a typical histological pattern of diabetic glomerulopathy [23]. It should, however, be noted that the fraction of patients with diabetic retinopathy at baseline was similar in the three urinary albumin excretion level groups (Table 1), thus indicating that the proportion of patients with typical diabetic glomerulopathy was the same in all three groups and that kidney function also can be preserved in these patients. Analysing only patients with retinopathy at baseline showed that the obtained urinary AER category was still a significant predictor for the annual decline in glomerular function ($P = 0.008$). It is also important to notice that even though the rate of decline in GFR diminished with remission to normoalbuminuria, it was not halted.

In conclusion, we have demonstrated that changes in urinary AER in microalbuminuric type 2 diabetic patients are closely related to changes in GFR. In order to diminish the deterioration of kidney function, efforts should be made to promote remission to normoalbuminuria in all these high-risk patients. The achievement of this goal can be facilitated by improved glycaemic regulation and early initiation of antihypertensive treatment, especially with a blockade of the RAS.

Conflict of interest statement. None declared.

References


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