Similar renal decline in diabetic and non-diabetic patients with comparable levels of albuminuria

Victor Lorenzo¹, Ramon Saracho², Javier Zamora³, Margarita Rufino¹ and Armando Torres⁴

¹Nephrology Section, Hospital Universitario de Canarias, Santa Cruz de Tenerife, La Laguna, ²Nephrology Division, Hospital de Santiago, Vitoria, Alava, ³Biostatistic Unit, Hospital Ramon y Cajal, Madrid and ⁴Research Unit, Hospital Universitario de Canarias, Santa Cruz de Tenerife. Fundación Reina Sofía de Investigación, Spain

Correspondence and offprint requests to: Victor Lorenzo; E-mail: vls243@gmail.com

Abstract

Background. Diabetes is the main cause of ESRD, and albuminuria is a major determinant of adverse renal outcome. Likewise, albuminuria is an intermediate risk factor of chronic kidney disease (CKD) progression in diabetic patients. Our aim was to compare the rate of renal decline in diabetic and non-diabetic CKD patients (GFR < 50 ml/min) with comparable levels of albuminuria.

Received for publication: 26.9.08; Accepted in revised form: 13.7.09

Nephrol Dial Transplant (2010) 25: 835–841
doi: 10.1093/ndt/gfp475
Advance Access publication 17 September 2009
Methods. In this observational study, 333 patients (age 67 ± 15 years, 46% diabetics) were included during a 7.5-year period. The mean follow-up was 30 ± 18 months (range 4–79). The influence of study variables was evaluated applying a time-dependent Cox model and slope-based outcome using a linear regression model.

Results. The diabetes condition was associated with adverse outcome in univariate analysis, and after adjusting for age, sex and systolic blood pressure. However, when controlling for albuminuria (a time-dependent covariate), diabetes did not show any association with outcome. In addition, the mean slope of renal decline was similar in diabetic and non-diabetic patients when controlling for albuminuria. The urinary albumin–creatinine ratio was a robust predictor of poor outcome in uni- and multivariate models. In the diabetic group, time-varying albuminuria did not influence renal outcome in the Cox model, and time-varying albuminuria remained a strong predictor of outcome.

Conclusions. Diabetic patients have a poorer renal outcome, but at comparable levels of albuminuria renal decline is similar in diabetic and non-diabetic patients. Albuminuria is a risk factor for renal decline, and the main target to delay progression in patients, diabetics or non-diabetics, with moderate to advanced CKD.

Keywords: albuminuria; chronic kidney disease; diabetes; renal disease progression

Introduction

Prospective studies have identified risk factors for chronic kidney disease (CKD) in the general population as well as risk factors for progression in patients with established chronic nephropathies [1]. Several demographic, comorbidity and biochemical factors may interact with pathophysiological mechanisms to accelerate progression [1,2]. Population-based studies have shown that diabetes is a relevant risk factor for CKD [3], and according to renal registry reports, diabetes is the single most common cause of end-stage renal disease (ESRD) worldwide [4,5]. One might infer from this information that diabetes per se is a predictor of unfavourable renal outcome. This inference, however, may be premature because diabetic patients have a marked heterogeneity in the underlying kidney lesion, and large inter-individual variation in the rate of progression has been reported. From the multiple factors that may affect this variation, urinary albumin excretion is recognized as a major risk factor [6–8].

High urinary albumin excretion is the most important mediator of progression to ESRD in experimental and clinical investigation [2,9,10], and numerous studies have shown the adverse effect of albuminuria in diabetic [3,6,7,11–13] and non-diabetic patients [10,14–16] with mild to moderate renal damage. However, all of these studies evaluated the effect of urinary albumin as a fixed covariate at baseline without considering the changes of this parameter over time. Moreover, no studies have compared the rate of progression of CKD in diabetic and non-diabetic patients with more advanced renal disease and with comparable levels of albuminuria.

Our aim was to clarify whether diabetes is a predictor of more rapid decline of renal function, in patients with moderate to severe CKD—glomerular filtration rate (GFR) <50 ml/min—while controlling for albuminuria. In order to check the robustness of our analytical approach, we applied two different multivariate models: a time-dependent Cox model to evaluate variation of relevant biochemical variables over time, and a slope-based outcome to compare renal function decline between groups.

Material and methods

Patients and data collection

We conducted a retrospective, longitudinal, observational study of incident patients with CKD (GFR<50 ml/min) referred to our nephrology clinic at the University Hospital of Canary Islands between January 2000 and July 2007. During this period, baseline and follow-up data were collected for 407 patients. The analysis was restricted to 333 patients who had more than three serum creatinine tests sufficient to calculate the rate of decline in kidney function.

Visits were scheduled every 2–4 months or more often if necessary. Patients received standard care. Sixty-four percent received angiotensin-II receptor enzyme inhibitors or angiotensin-II receptor antagonists or both as antihypertensive and renoprotective medication. Most patients were receiving this medication at entry, and continued receiving these drugs during the follow-up period with dose adjustment as required. Criteria applied for the initiation of dialysis were based on clinical and biochemical data. Diabetes as primary disease or the rate of albuminuria was not considered criteria for early dialysis initiation.

Patient characteristics at baseline were collected from electronic medical records including demographic data, body mass index (BMI, kg/m²), cardiovascular comorbidity—defined as history of congestive heart failure and/or coronary, cerebral or peripheral vascular disease—and smoking status. Smoking status was categorized into two levels: never-smoker and active or previous smoker. Also, baseline and follow-up laboratory measurements and blood pressure were recorded. Patients were followed until dialysis initiation, death, loss of follow-up or until 31 July 2007. Patients were considered as lost to follow-up when they had no contact with the medical centre for >6 months.

Primary renal diseases were diabetes-related ESRD 46%, chronic glomerulonephritis 7.5%, ischaemic or vascular nephropathy 18%, polycystic renal disease 5.1%, chronic interstitial nephropathy 7.5%, unknown 9.3%, and other causes represented <5%. Patients were considered to be diabetic if they had a history of diabetes mellitus and were taking hypoglycaemic medication, mostly insulin. The diagnosis of diabetes was made previously by their family doctor or the by an endocrinologist. For the purpose of this study, patients were classified as diabetic or non-diabetic, and the specification of diabetic nephropathy—which requires the presence of albuminuria—was not the issue. We applied this concept to evaluate the independent effect of diabetes per se on renal outcome, apart from the influence of albuminuria.

Laboratory methods

All laboratory measurements were performed by our University Hospital laboratory using standardized and automated methods. Creatinine was measured using an enzymatic commercial kit-Crea Plus (Roche Diagnostics, Meylan, France). Albuminuria was measured using immunoturbidimetric assay (Roche Diagnostics, France).

GFR was calculated using the Modification of Diet in Renal Disease (MDRD) study four-item equation ([186.3 × (serum creatinine) 1.154 × (age) 0.203 × 0.742 (if female)]) [17]. More than three GFR measures during the study period were required to estimate the GFR slope. The regression coefficient of time against GFR was used to give an estimated rate of GFR decline in millilitre per minute per 1.73 m²/year for each individual patient. Urinary albumin–creatinine ratio (mg/g), serum albumin and hae-
Table 1. Patient characteristics grouped according to diabetes status

|                        | All patients | Diabetics | Non-diabetics | P     |
|------------------------|--------------|-----------|---------------|-------|
| Number (%) of patients | 333          | 153 (46)  | 180 (54)      | 0.058 |
| Age (years)            | 66.8 ± 14.5  | 66.3 ± 12.3| 67.2 ± 16.2   | 0.458 |
| Gender (% males)       | 61           | 61        | 65            | 0.427 |
| CV comorbidity (%)     | 45.9         | 57.5      | 42.8          | 0.0008|
| MDRD_t0 (ml/min)       | 24.7 ± 7.4   | 25.4 ± 7.7| 24.1 ± 7.1    | 0.130 |
| Time-to-event (months) | 30.0 ± 18.2  | 28.1 ± 18.2| 31.6 ± 18.1   | 0.080 |
| MDRD slope (ml/min/year)| -4.6 ± 5.7  | -6.0 ± 5.7| -3.5 ± 5.4    | 0.001 |
| Ur Alb:Cre ratio (mg/g)| 1026 (242–2312)| 1290 (816–3978)| 476 (105–1597)| 0.001 |
| SBP (mmHg)             | 139 ± 15     | 143 ± 14  | 136 ± 15      | 0.001 |
| DBP (mmHg)             | 76 ± 9       | 75 ± 9    | 76 ± 8        | 0.310 |
| sAlb (g/dl)            | 3.9 ± 0.5    | 3.7 ± 0.5 | 4.1 ± 0.4     | 0.001 |
| Haemoglobin (g/dl)     | 11.9 ± 1.6   | 11.7 ± 1.5| 12.1 ± 1.7    | 0.020 |
| DPI (g/kg id_bw)       | 1.00 ± 0.23  | 1.04 ± 0.24| 0.96 ± 0.21   | 0.008 |
| BMI (kg/m²)            | 28.1 ± 4.6   | 28.8 ± 4.6| 27.4 ± 4.5    | 0.009 |
| RAS blockers (%)       | 63.7         | 75.8      | 53.3          | 0.001 |
| Smoking status (%)     | 48.0         | 49.0      | 47.2          | 0.743 |
| HDL-C (mg/dl)          | 53 ± 16      | 51 ± 15   | 54 ± 16       | 0.177 |
| LDL-C (mg/dl)          | 106 ± 38     | 103 ± 40  | 109 ± 37      | 0.133 |

Molecular variables were recorded at baseline, and also analysed as time-varying repeated measures. The urinary albumin:creatinine ratio was measured in the first morning sample in the majority of cases. In a few cases where a first morning sample was not available, it was obtained from a random sample.

Dietary protein intake was assessed by 24-h urine nitrogen excretion according to the method described by Maroni et al. [18], as follows: Estimated protein intake (g/day) = 6.25 × Urinary Urea Nitrogen (g/day) + 0.031 × Ideal body weight (kg).

Statistical analysis

For univariate analyses, the chi-square test was used to assess the association between categorical variables. Differences in continuous variables between diabetic status groups were performed with the Student’s t-test. Survival curves were estimated by the Kaplan–Meier method, and differences between curves were evaluated with the log-rank test.

We used multivariate Cox proportional-hazard regression to assess the relationship of diabetes as independent variable with the time to initiation of dialysis (i.e. dialysis-free survival) after adjusting for age, gender, mean systolic blood pressure (SBP), MDRD at entry, baseline data of cardiovascular comorbidity (present/absent), BMI, lipid profile, estimated protein intake, smoking status and renin–angiotensin system blocker medication. All variables significantly associated with the outcome in the univariate analyses were considered in the maximum multivariate model as well as corresponding interaction terms. A manual backward modelling strategy was used to eliminate variables from the maximum model in order to obtain the most parsimonious model to assess the effect of the independent variables on outcome. We tested the proportional hazard assumption by examining log (t-log) survival plots for different categories against time. Since death may be a competing event for ESRD, especially in elderly patients, in a secondary analysis we expanded the definition of the outcome to include death as an event. To consider the variation of relevant biochemical parameters over time, the following variables were included as time-varying indicators: urinary albumin:creatinine ratio, serum albumin and serum haemoglobin. The time-dependent Cox regression was modelled as follows: two measures per year for a 2-year period were computed for each individual patient, averaging all repeated measures within a 26-week interval. We imputed missing data for urinary albumin:creatinine ratio (2.4% of the cases), serum albumin (4.8%) and haemoglobin (3.6%) using the mean of nearby values. In addition, MDRD at entry, diabetes, age and mean SBP were included in the model as fixed covariates. After excluding patients who died or were lost to follow-up during the 2-year observation period, the final number of patients for this analysis was 215.

Finally, given that albuminuria may be part of the causal pathway between diabetes and renal outcome, this parameter should be considered an intermediate risk factor, instead of a confounding variable [19]. For this reason, we repeated the multivariable Cox model and regression analysis without including this parameter as a covariate.

All tests were two-tailed and a significance level of 5% was established. Statistical analyses were performed using the SPSS 13.0 statistical package for Windows (SPSS Inc, Chicago, IL).

This study was approved by the ethics committee of the University Hospital and was conducted in accordance with the provisions of the Declaration of Helsinki.

Results

Three hundred thirty-three patients were followed for a mean period of 30 ± 18 (range 4–79) months. Demographic data, clinical parameters and baseline biochemical characteristics were tabulated according to diabetes status (Table 1). During the follow-up, 134 patients (40%) initiated dialysis, 26 (8%) died, 12 (4%) were lost to follow-up and 4 (1%) received pre-emptive kidney–pancreas transplantation. The median number of MDRD determinations per patient during the study period was 11 (range 4–45, mean 13). Of note, 39 patients (12%) showed improvement in renal function during the follow-up period; the median age of this group was 78 years and the median urinary albumin:creatinine ratio was 157 mg/g.
In the univariate analysis, diabetes and a higher urinary albumin:creatinine ratio were associated with poor outcome. Figure 1 shows Kaplan–Meier estimates of dialysis-free survival according to the urinary albumin:creatinine ratio. This parameter was divided into three groups: group 1: <300 mg/g (microalbuminuria range), group 2: 300–1500 mg/g and group 3: >1500 mg/g (1500 mg/g being the median value of the macroalbuminuria range). Younger age, male sex, SBP, lower serum albumin and lower haemoglobin (data not shown) were also associated with poor outcome. As expected, MDRD at entry was clearly linked to outcome ($P < 0.0001$)—the higher the baseline MDRD, the longer the dialysis-free survival time. All these covariates were included in the multivariate models.

Four parameters related to blood pressure were analysed: SBP and diastolic blood pressure, pulse pressure and mean number of antihypertensive drugs. Given that these variables are closely related, only the most significant variable—SBP—was included in the analyses.

To better illustrate the strong influence of albuminuria on renal outcome, patients were divided into four groups based on two parameters: diabetes (yes/no) and urinary albumin:creatinine ratio (above or below median cut-off). We clearly observed that patients with higher levels of albuminuria (the median urinary albumin:creatinine ratio >1030 mg/g), with or without diabetes, showed significantly poorer renal outcome. At 2 years of follow-up, the median dialysis-free survival time was approximately 90% for the lower albuminuric group versus 50% for the higher albuminuric group, and very similar for diabetic and non-diabetic patients in both groups (Figure 2).

Other parameters of interest were tested as potential predictors. Smoking status was not related to age or diabetes, but it was highly related to gender—91% of smokers were males. We did not observe an independent effect of smoking on outcomes, either in the total group or in the male group. BMI was significantly higher in diabetic patients, but was similar in age and sex groups, and had no effect on renal outcome in univariate analysis. Baseline data of lipid profile (HDL and LDL cholesterol) were not associated with greater hazard for renal end points. Dietary protein intake, indirectly evaluated by urinary urea nitrogen excretion, was slightly higher in diabetic than in non-diabetic patients, but similar in sex and age groups. The presence of cardiovascular comorbidity at entry did not influence renal outcome. All these previous variables, when tested in multivariate analysis, failed to have a significant effect on renal outcome and were not included in the final model.

We explored several multivariate models (Table 2). In model 1, we evaluated the effect of diabetes on dialysis-free survival time, adjusting for age, sex and MDRD at entry; and in model 2, the additional effect of SBP was tested. In both models, we observed that diabetes was independently associated with faster progression of CKD. Age and gender did not show interaction with diabetes. In the next two models, we also included the effect of serum albumin and a urinary albumin:creatinine ratio as time-varying indicators. After adjusting for age, gender, SBP, MDRD at entry, urinary albumin:creatinine ratio and serum albumin, diabetes did not show any influence on outcome (Table 2). The time-dependent model revealed that, when taking into account the longitudinal variation of urinary albumin over time, diabetes per se did not show any influence on outcome, while albuminuria proved to be the strongest predictor of progression.

When we used the combined outcome ESRD and death as dependent variables, the result proved to be closely related. The only difference was the age variable that was no longer statistically associated with outcome.

Finally, we performed a subgroup analysis among diabetic patients to evaluate the influence of glycosilated haemoglobin (HbA1c) on renal outcome. The median level of HbA1c was 7.2% with an interquartile range of 6.4–8.0. After adjusting for confounders, HbA1c values analysed as a time-varying indicator in the Cox model did not show any influence on outcome (data not shown).

Applying multivariate regression model, the effect of the independent variables was similar to that observed using Cox models. The mean decline in renal function was faster in diabetic versus non-diabetic patients after adjusting for
age, sex, MDRD at entry and SBP (Table 3, models 1 and 2). Again, the effect of diabetes disappeared when the urinary albumin:creatinine ratio and serum albumin at baseline were included in the models (3 and 4). Albuminuria remained the strongest predictor of progression.

To emphasize the determinant influence of albuminuria on progression, the mean rate of renal decline in patients grouped according to diabetes status and ranges of albuminuria has been shown in Figure 3. At the three ranges of the albumin:creatinine ratio, the slope of renal decline was similar for diabetic and non-diabetic patients. Interestingly, patients with an albumin:creatinine ratio in the microalbuminuria range (<300 mg:g) showed a slope of 1.2–1.4 ml/ min/year, demonstrating that in patients with GFR < 50 ml/ min, diabetic or not, values in microalbuminuria range were also associated with renal decline.

**Discussion**

This longitudinal observational study highlights the importance of albuminuria as the single most powerful predictor of faster progression in patients with CKD and GFR < 50 ml/min. However, our results challenge the assumption that diabetes per se is a predictor of adverse outcome. At comparable levels of albuminuria the evolution of CKD was similar in patients with and without diabetes, and this observation was confirmed applying a time-dependent Cox model and slope-based outcome. This analysis verified that diabetics showed faster renal decline when compared with non-diabetic patients, but this is explained by their generally higher rates of urinary albumin.

Several previous studies have clearly shown that the rate of albuminuria predicts outcome in diabetic [6–8,11–13,20] and in non-diabetic patients [10,14–16]. Likewise, some population-based studies have demonstrated that di-

### Table 2. Time-dependent Cox model

| Effect of diabetes | Effect of Ur Alb:Cre ratio |
|-------------------|---------------------------|
| Dependent variable: Dialysis-free survival (months) | | |
| Models | Exp (B) (95% CI), Sig | Exp(B) (95% CI), Sig |
| M1. Diabetes + age + sex + MDRD_t0 | 1.83 (1.29:2.58), P < 0.001 | |
| M2. M1 + SBP | 1.52 (1.08:2.16), P < 0.020 | |
| M3. M2 + time-var Ur Alb:Cre ratio | 1.30 (0.81:2.10), P = 0.279 | 1.37 (1.27:1.49), P < 0.001 |
| M4. M3 + time-var sAlb | 1.09 (0.66:1.83), P = 0.732 | 1.30 (1.16:1.47), P < 0.001 |

Time-var: time-varying indicators.

For abbreviations see Table 1.

Model 1: we evaluated the effect of diabetes on dialysis-free survival time, adjusting for age, sex and MDRD_t0.

Model 2: the additional effect of SBP was tested.

Models 3 and 4: we also included the effect of urinary albumin:creatinine ratio and serum albumin using repeated measures.

### Table 3. Multivariate linear regression analysis was used to model the decline of renal function

| Effect of diabetes | Effect of Ur Alb:Cre ratio |
|-------------------|---------------------------|
| Dependent variable: Slope of renal decline (ml/min/year) | | |
| Models | β (95% CI), Sig | β (95% CI), Sig |
| M1. Diabetes + age + sex | 2.54 (1.38:3.71), P < 0.001 | |
| M2. M1 + SBP | 2.20 (0.82:3.21), P < 0.001 | |
| M3. M2 + Ur Alb:Cre ratio | 0.45 (−0.79:1.70), P = 0.713 | −1.21 (−1.59:−0.83), P < 0.001 |
| M4. M3 + sAlb | 0.04 (−1.19:1.27), P = 0.946 | −0.81 (−1.23:−0.39), P < 0.001 |

A negative beta coefficient indicates that the higher the value of the numerical variable, the steeper the slope of renal function decline over time. The urinary albumin:creatinine ratio was log-transformed to obtain the normal distribution of the data.

For abbreviations see Table 1.

Model 1: we evaluated the effect of diabetes, age and sex on the slope of renal decline.

Model 2: the additional effect of SBP was tested.

Models 3 and 4: we also tested the effect of urinary albumin:creatinine ratio and serum albumin, respectively.

**Fig. 3.** Mean slope of renal decline in diabetic and non-diabetic patients separated according to the urinary albumin:creatinine ratio (three groups). Results are expressed as mean and standard error. Number of patients appears in brackets.
abetes is a risk factor for moderate CKD [3] or for rapid deterioration in patients with more advanced renal disease [21], but the influence of albuminuria was not considered in these reports. In this last-cited study [21], diabetes was associated with poor renal outcome, but data on albuminuria were not provided, and the terms diabetes and diabetic nephropathy were used indiscriminately. The particular aim of our study was to evaluate the independent influence of diabetes itself on renal outcome, in patients with more advanced CKD, after controlling for albuminuria. A notable finding was that, although in the univariate model the mean GFR decline was significantly faster in diabetic than in non-diabetic patients (6.0 ± 5.7 versus 3.5 ± 5.4 ml/min/year respectively), the multivariate analyses demonstrated that diabetes was only related to faster renal deterioration when associated with higher rates of urinary albumin excretion.

Applying the multivariate Cox model to diabetic and non-diabetic patients separately, we observed that albuminuria adversely affected the rate of progression to the same extent in both groups. An identical observation was made by Ruggenenti et al. [22] in a study designed to evaluate intensified multi-drug treatment on residual proteinuria: GFR decline was dependent upon the amount of residual proteinuria, regardless of diabetes status.

Previous studies have shown that urinary albumin, even in the microalbuminuric range, is a predictor of renal function impairment in the general population [12,23]. This observation was verified in our study, in patients with moderate to advanced renal damage. On the other hand, patients with high levels of albuminuria, irrespective of the presence of diabetes as the primary disease, showed a faster rate of decline.

The effect of diabetes control evaluated by glycosilated haemoglobin is controversial. Hsu et al. [3] found that type 2 diabetic patients with higher baseline levels of HbA1C had an increased risk for developing moderate CKD, even in the absence of albuminuria. In contrast, other studies did not find an association between baseline HbA1C level and renal outcome [20,24]. In agreement with these findings, our analysis failed to demonstrate an association between HbA1C levels and CKD progression. It should be noted that in our analysis, HbA1C was evaluated as a time-varying indicator and in patients with more advanced renal damage.

In addition to urinary albumin, other demographic and clinical parameters were evaluated as potential confounders. Younger age and male sex were associated with poor outcome in all models. Similar results were previously observed in population-based studies [21,25]. It is remarkable that the influence of age disappeared when the end point was the composite of dialysis-free survival and death, showing that ESRD and death were competing factors for older patients. In addition to these parameters, we substantiated the influence of SBP [16,26–29] as a major predictor of CKD. Serum albumin and haemoglobin were also included in our multivariate analysis. These parameters have demonstrated their influence on renal decline in specific populations and occasionally yielded conflicting results [11,30]. Serum albumin has been reported as a predictor of adverse outcome [11,31], independently of, and complementary to albuminuria, and an identical association was obtained in the present study. However, we did not find an association between haemoglobin and outcome. It is possible that our patients, aggressively treated with erythropoietin (target haemoglobin levels of 12–13 g/dl), were situated in a narrow window of values. In fact, the median and inter-quartile range of haemoglobin values were 11.9 g/dl and 10.8–13.1 g/dl, respectively.

Not surprisingly, the proportion of patients receiving RAS blockers was higher in diabetic patients (Table 1). Although, the use of RAS blockers could have some beneficial effect, patients using these drugs—and in spite of them—were more proteinuric. For this reason, when RAS blocker medication was tested in the multivariate analysis, these drugs did not influence outcome [HR 1.29 (CI 95% 0.87–1.9), P = 0.199], the rate of residual urinary albumin remaining as the most powerful predictor.

Limitations and strength of the study
Our study was performed in patients with a GFR < 50 ml/min, so conclusions based on these results cannot be applied to patients at earlier stages of CKD. Due to the retrospective nature of the study, associations but not causality can be established. A potential limitation is the uncertain fate of patients who were lost to follow-up, but a reanalysis of data excluding these patients did not significantly alter the outcomes (data not shown). Ethnicity was not considered because all patients were Caucasian; thus, these results may not be applicable to other ethnic groups.

A shortcoming of the study was the uncertainty of the type of nephropathy in diabetic patients. This diagnosis was clinical, based on the presence of albuminuria, and renal biopsy is not currently prescribed. Obviously, the presence of diabetic nephropathy and its magnitude influence the rate of progression, but this was not the issue in this study. Our purpose was to determine whether renal outcome differed between patients with and without diabetes, at similar rates of albuminuria. Regarding the type of diabetes, previous studies have shown similar rates of progression in type 1 and type 2 diabetes [6,32]. Only a small number of patients were type 1, and the influence of the type of diabetes was not an objective of the study.

The strength of our study includes the application of two different models, and the role of studied parameters was verified in both models. Virtually, all previous studies have examined associations between albuminuria at baseline and renal outcome, without accounting for the changes of these measures during the follow-up. We increased the robustness of our observations using time-dependent models. This approach offers more realistic information about parameters that change over time than analyses restricted to fixed baseline data.

In conclusion, diabetes is the main cause of ESRD and albuminuria the major risk factor for renal decline. In patients with moderate to severe CKD, renal decline is similar in diabetic and non-diabetic patients with comparable levels of urinary albumin.
Albuminuria, but not diabetes, predicts progression

Acknowledgement. We wish to thank Michael McLean for his assistance in the preparation of the text.

Conflict of interest statement. None declared.

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Received for publication: 29.3.09; Accepted in revised form: 18.8.09