Diabetic nephropathy in 27,805 children, adolescents and adults with type 1 diabetes: effect of diabetes duration, HbA1c, hypertension, dyslipidemia, diabetes onset and gender

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Running title: Nephropathy and risk factors in Germany and Austria

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Received for publication 11 February 2007 and accepted in revised form 9 July 2007.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.
Abstract

OBJECTIVE: To give an up to date profile of nephropathy and involvement of risk factors in a large, prospective cohort of patients with type 1 diabetes and largely pediatric and adolescent onset of disease.

RESEARCH DESIGN AND METHODS: 27,805 patients from the nationwide, prospective DPV-survey were included in the present analysis. Inclusion criteria were at least two documented urine analysis with identical classification. Urine analysis, treatment regimens, diabetes complications and risk factors were recorded prospectively. Baseline characteristics were: age at diagnosis 9.94 yrs (median; interquartile range 5.8-14.3), age at last visit 16.34 yrs (12.5-22.2) and follow up time 2.5 yrs (0.43-5.3). Cumulative incidence of nephropathy was tested by Kaplan-Meier analysis, association with risk factors by logistic regression.

RESULTS: Nephropathy was classified as normal in 26,605, microalbuminuric in 919, macroalbuminuric in 78 and end stage renal disease (ESRD) in 203 patients. After calculated diabetes duration of 40 years, 25.4% (95% confidence interval 22.3-28.3) had microalbuminuria and 9.4% (8.3-11.4) macroalbuminuria or ESRD. Risk factors for microalbuminuria were diabetes duration (odds ratio 1.033, p< 0.0001), HbA1c (1.13, p< 0.0001), LDL-cholesterol (1.003, p< 0.0074) and blood pressure (1.008, p< 0.0074), while childhood diabetes onset (1.011, p< 0.0001) was protective. Male gender was associated with development of macroalbuminuria.

CONCLUSION: Diabetes duration, HbA1c, dyslipidemia, blood pressure and male gender were identified as risk factors for nephropathy. Therefore, beside best possible metabolic control, early diagnosis and prompt treatment of dyslipidemia and hypertension is mandatory in patients with type 1 diabetes.
Micro- and macroalbuminuria are important markers for early and progressive diabetic kidney disease. Patients with type 1 diabetes face a 20 – 50% probability to develop end stage renal disease (ESRD) requiring dialysis or renal transplantation (1). But over the last decades, cumulative incidence of nephropathy has further declined, which was attributed to intensified treatment regimens and a more aggressive therapy of hypertension and dyslipidemia (1,2).

Since the 1980s, microalbuminuria has been established as an early marker of progressive kidney disease in diabetes (3), starting at pediatric age (4,5) and until now, albumin excretion rate (AER) remains the best available of non-invasive predictors for diabetic nephropathy and should be measured regularly according to established guidelines (6-8).

Since the Diabetes Control and Complications Trial (DCCT), glycemic control was established as the dominant risk factor for development of diabetic nephropathy (9). Moreover, the DCCT follow up study Epidemiology of Diabetes Interventions and Complications (EDIC) has demonstrated a persistent delay of progression of diabetic nephropathy 7 to 8 years after the end of the DCCT, in the previously intensively treated patients (10).

Next to HbA1c, presence of retinopathy, smoking, dyslipidemia, hypertension and male gender have previously been reported as risk factors for progression towards diabetic nephropathy in patients with type 1 diabetes (11-14). In adults, microalbuminuria and the risk factors hypertension, smoking and poor glycemic control predict increased risk for cardiovascular disease and early mortality (15,16). In diabetes with childhood onset, young age at diagnosis and a longer, prepubertal run, seem to delay the time until microalbuminuria will develop, a phenomenon that is not yet understood (17,18).

The aim of this study was firstly, to analyze the prevalence of nephropathy in a nationwide, prospective survey including children, adolescents and adults with type 1 diabetes from Germany and Austria. Secondly, risk factors with suggested or proven evidence for involvement in diabetic nephropathy were tested for its association with micro- and macroalbuminuria.

**RESEARCH DESIGN AND METHODS**

The German Diabetes Documentation System (DPV) is a prospective, nationwide survey of demographic, anthropometric and diabetes-related characteristics of patients with type 1 diabetes (19,20). Local data control authorities approved data collection and anonymous analysis for study purposes; participating centers were listed in the appendix (available at http://care.diabetesjournals.org). Data acquisition for the present analysis was done until February 2007 and included a total number of 27,805 children, adolescents and adults with type 1 diabetes being consecutively registered at 262 centers for pediatric or adult diabetes care. The following independent risk factors for development of nephropathy were analyzed by logistic regression and stepwise selection of parameters: diabetes duration, age at diagnosis, gender, blood pressure, HbA1c, dyslipidemia, cumulative HbA1c and smoking.

**Assessment of nephropathy**

Screening for microalbuminuria was performed by the following methods: 1) measurement of the albumin-to-creatinine ratio in a random spot collection; 2) 24-h collection with creatinine; and 3) timed (e.g. overnight) collection. Microalbuminuria or macroalbuminuria was defined as at least two increased urine albumin tests during follow up period. Within the most recent year, albuminuria was determined by albumine-creatinine ratio in 12.1%, albumine excretion rate (24 hrs) in 31.7% and albumine concentration in timed, overnight collection in 56.2%. Thresholds were albumin excretion rate (AER) ≥ 20µg/min or a urine albumin/ creatinine ratio (UAC) ≥ 2.5 mg/mmol according to guidelines of ADA (21). Macroalbuminuria was defined as AER ≥
≥ 200 µg/min or an UAC ≥ 35 mg/mmol. Albumin and creatinine was measured by the center specific laboratory methods that had to meet German internal and external quality requirements for laboratory analysis. Patients with ESRD (requiring dialysis/transplantation) were included in Kaplan-Meier survival analysis to adequately reflect prevalence of severe nephropathy, but were excluded from regression analysis for macroalbuminuria-associated co-variates.

**Risk factors for diabetic kidney disease**

**HbA1c.** Glycemic control was assessed as mean HbA1c during follow up period. Single center HbA1c methods were standardized according to the DCCT reference range of 4.05 – 6.05% (22).

**Hypertension.** Systolic and diastolic blood pressure was measured according to current guidelines. Age specific normal values were obtained from the Task Force on Blood Pressure Control in Children and Adolescents (23). Hypertension was defined as the median value > 95th percentile of at least three independent measurements. Hypertension was classified as a dichotomous variable in macroalbuminuric patients, but as a continuous variable (systolic and diastolic blood pressure) in the large cohorts of normoalbuminuric and microalbuminuric patients.

**Dyslipidemia.** Dyslipidemia was diagnosed if at least one lipid parameter was permanently increased. Cut offs were for total cholesterol > 200 mg/dl, LDL cholesterol >160 mg/dl and triglycerides > 150 mg/dl. In logistic regression analysis for microalbuminuria, triglycerides, HDL- and LDL-cholesterol were treated as independent, continuous variables, whereas for macroalbuminuria as dichotomous variable “dyslipidemia”.

**Smoking.** Smoking habits were asked for at each single visit. If at least one cigarette per day was reported, patients were classified as smokers.

**Pharmacotherapy.** Patients with dyslipidemia and systolic or diastolic hypertension were treated with lipid-lowering or antihypertensive drugs. Used lipid lowering drugs were statins, fibrates or cholesterol absorption inhibitors such as ezetimibe. Treatment with antihypertensive drugs were classified and documented as angiotensin converting enzyme (ACE) inhibitors, angiotensine receptor blockers (ARBs), β-blockers, diuretics, and calcium channel blockers. Pharmacotherapy with these respective drugs was documented in a qualitative fashion.

**Statistical analysis**

The SAS 9.1 statistic software package was used for data evaluation and statistical analysis. In detail, relative contribution of covariates to risk for nephropathy was analyzed by logistic regression and stepwise selection of parameters, Kaplan-Meier method for survival analysis, and the log-rank-test for trend. Differences between groups of normoalbuminuria, microalbuminuria and overt nephropathy were analyzed by non-parametric Mann-Whitney-test (Tab.1). The Odds Ratio (OR) and 95% Wald confidence limits are reported for logistic regression analysis and data were corrected for use of antihypertensive and lipid lowering drugs. Data are presented as means and standard error where appropriate.

**RESULTS:**

**Cohort characteristics**

The study cohort was analyzed in February 2007 from 262 diabetic centers in Germany and Austria with a total number of 49,027 patients with type 1 diabetes being continuously followed in DPV. At time of analysis, 27,805 patients had at least two documented urine tests with clear result of normal or albuminuric reading in at least two follow up visits and gave consent for scientific data evaluation. We assume that the cohort analyzed is representative for all patients followed in DPV, as HbA1c (mean; included 7.99% vs. all 7.92%), male gender (52.5 % vs. 51.9%), age (21.1 yrs vs. 21.4 yrs), diabetes duration (8.3 yrs vs. 7.8 yrs) and age at diabetes onset (12.9 yrs vs. 13.6 yrs) was largely comparable. Characteristics of the analyzed cohort were: follow up time 2.5 yrs (median; interquartile range 0.5 –
5.3), 12.0 follow up visits (3.0 – 26.0), 9.0 HbA1c determinations (9 - 21) and 12 blood pressure measurements (3.0-26.0). Age at most recent visit (Fig.1A) and age at diagnose (Fig.1B) are predominantly in the pediatric and adolescent age. At their most recent visit, normal urine tests were found in 26,605 patients (95.6%) and at least two abnormal urine tests in 1200 patients (4.3%). Among the latter group, 281 of 1200 (23.4%) had at least two urine tests in the defined range of macroalbuminuria (AER > 200 µg/min, UAC > 35 mg/mmol/l) or ESRD with ongoing dialysis or after renal transplantation. In detail, 52 patients were macroalbuminuric alone and 229 proceeded towards ESRD. Comparing patients with normoalbuminuria and micro- or macroalbuminuria, the variables HbA1c, systolic and diastolic blood pressure, tobacco consumption and serum lipids, including cholesterol, LDL-cholesterol and triglycerides, were found higher in patients with increased albumin excretion (Tab.1). But these changes went parallel with increasing age, changed insulin treatment regimens and longer diabetes duration and therefore these findings were only noticed in a descriptive fashion. Treatment with antihypertensive drugs increased with severity of nephropathy, but still was unacceptable low in patients with micro- or macroalbuminuria (Tab.1).

Survival analysis of micro- and macroalbuminuria
Kaplan-Meier analysis revealed that after median diabetes duration of 40 years 25.4 % (95% confidence interval 22.3-28.3) of patients had microalbuminuria and 9.4 % (8.3-11.4) macroalbuminuria or ESRD (Fig 2). To describe the long term influence of HbA1c on nephropathy, patients were stratified into two groups – one with HbA1c levels above and one with HbA1c levels below 7.5%. The group above 7.5% developed microalbuminuria (Log rank test, \( \chi^2 \) 51.6, P<0.0001) and macroalbuminuria (Log rank test, \( \chi^2 \) 8.2, P<0.0042) significantly earlier than those below 7.5% (Figs. 3A and 3B). Differences between groups became evident after diabetes duration of approximately 10 years for microalbuminurua and 20 years for macroalbuminuria.

Nephropathy and age, gender, smoking and onset of diabetes
Logistic regression analysis with stepwise selection of parameters identified diabetes duration, dyslipidemia, and mean HbA1c as significant risk factors for development of microalbuminuria. When blood pressure and lipid levels were analyzed as continuous variables, and not as dichotomous cut off levels, systolic and diastolic blood pressure, but also triglyceride and LDL-cholesterol concentration, became independent and significant risk factors for development of microalbuminuria. In the relatively small number of patients with macroalbuminuria, diabetes duration, HbA1c, male gender and dyslipidemia were associated with development of overt nephropathy. Also young age at diagnosis reduced risk of microalbuminuria, when adjusted for diabetes duration and other independent co-variates (Table 2). Smoking and gender were included in stepwise selection of potential risk factors, but only male gender was associated with development of macroalbuminuria.

CONCLUSIONS
We analyzed prevalence of incipient and overt nephropathy in a large cohort of 27,805 children, adolescents and adults with type 1 diabetes. These data give a representative and up to date profile of diabetic nephropathy and associated risk factors in Germany and Austria. Detailed analysis of risk factors is of particular importance, as these could be influenced and controlled during diabetes follow up. Within 40 years of diabetes disease, calculated prevalence was 25.4% for persistent microalbuminuria but less than 10% for macroalbuminuria or end stage renal disease. This is a lower rate of nephropathy than reported earlier from cohorts followed in Denmark, England and Western Australia, with similar age of patients (11,24,25). Most
prominent difference in our study was a lower HbA1c level compared to these studies. But finally many factors, including cohort characteristics and study design, could explain deviating cumulative incidence of nephropathy.

In our study, microalbuminuria was associated with higher HbA1c, serum lipids, in detail LDL-cholesterol and triglyceride, systolic and diastolic blood pressure, but also with older age at diagnosis. Macroalbuminuria, documented in a much smaller number of patients, was linked to HbA1c, dyslipidemia and male gender. Increased HbA1c as a marker of chronic hyperglycemia is the most established and unquestioned risk factor for diabetic kidney disease in adult and pediatric onset type 1 diabetes (11,13,14,25). DCCT and the follow up study EDIC clearly demonstrate that previous intensive treatment of diabetes with near-normal glycemia has an extended benefit in delaying development and progression of diabetic nephropathy (9,10). By Kaplan-Meier-analysis, we found that a cumulative HbA1c of more than 7.5% significantly raised the probability of micro- and macroalbuminuria. This effect became evident after diabetes duration of more than 10 years for microalbuminuria and more than 20 years for macroalbuminuria. Therefore, efforts to normalize metabolic control should be started right from diabetes onset, although consequences on renal function might not be seen before adult age.

We found both systolic and diastolic blood pressure to be independently associated with microalbuminuria. Hypertension per se was not an independent risk factor for nephropathy and was lower in patients with macroalbuminuria or dialysis. This fact might reflect strict antihypertensive treatment regimens in patients with advanced renal disease. But whether or not blood pressure is cause or result of nephropathy, hypertension should strictly be treated, also in pediatric and adolescent patients (26).

Dyslipidemia, in detail increased LDL cholesterol, is associated with progression of diabetic kidney disease (12,27). We found that both LDL-cholesterol and triglyceride are independently associated with microalbuminuria. Furthermore, association between serum advanced glycation end products (AGEs) and increased serum cholesterol imply involvement of lipids in formation of AGEs and by this way, in renal disease (28).

Rate of smokers among patients with type 1 diabetes is alarmingly high, in detail 10.5% of adolescents and 34.8% of young adults in Germany and Austria (29), but whether smoking is a risk factor for development or progression of diabetic kidney disease, has recently been discussed controversially (13,30,31). We did not find that smoking increased likelihood of nephropathy, but programs to keep children and adolescents away from starting smoking should be an important factor of continuous diabetes care, first of all to prevent macrovascular disease (15,16).

Gender influence on nephropathy has been found to be age dependent. In adolescents, female gender increases risk of microalbuminuria (14,25), while in adults and in terms of advanced nephropathy, men are at higher risk to develop renal disease, also if data were adjusted to social class, HbA1c, smoking and blood pressure (11,16).

We found no link between gender and microalbuminuria, but higher risk for macroalbuminuria in males.

Several studies indicated, that prepubertal duration of diabetes delays onset of diabetic nephropathy. In our study, microalbuminuria was delayed by very early onset of diabetes and confirmed these previous, prospective studies (14,32,33). We do not suggest, that poor metabolic control in prepubertal children does not add to the risk of microvascular complications, but there is evidence that it does so at a smaller rate (34).

In conclusion, diabetes duration, long-term metabolic control (HbA1c), dyslipidemia and male gender have been identified as independent risk factors for development of nephropathy in this large cohort. We conclude from our data, that diabetes care must continue to focus on long term metabolic control, but also on reduction of
additional risk factors, like dyslipidemia and blood pressure.

**ACKNOWLEDGMENTS:**
We kindly acknowledge to each of the 262 participating Diabetes Centers in Germany and Austria. These centers are listed in the e-appendix. Financial support by German Ministry of Health, German Diabetes Association, German Diabetes Foundation, Bundesärztekammer, Nationales Aktionsforum Diabetes mellitus, Dr-Bürger-Büsing-Foundation and Novo Nordisk Germany.
Reference List


32. Donaghue KC, Fairchild JM, Craig ME, Chan AK, Hing S, Cutler LR, Howard NJ, Silink M: Do all prepubertal years of diabetes duration contribute equally to diabetes complications? *Diabetes Care* 26:1224-1229, 2003

### Tables

**Table 1**—Clinical and laboratory characteristics of the 27,805 patients with type 1 diabetes from 262 centers included into nephropathy evaluation.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Nephropathy</th>
<th></th>
<th>P ***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26644</td>
<td>919</td>
<td>52 / 229</td>
<td></td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>52.6</td>
<td>52.1</td>
<td>58.0</td>
<td>ns</td>
</tr>
<tr>
<td>Age at last visit (yrs)</td>
<td>21.1 (0.09)</td>
<td>28.7 (0.64)</td>
<td>37.2 (1.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>8.3 (0.054)</td>
<td>12.6 (0.39)</td>
<td>20.1 (0.86)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>12.9 (0.07)</td>
<td>16.1 (0.45)</td>
<td>17.2 (0.78)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Insulin dose (IE/kg/d)</td>
<td>0.80 (0.002)</td>
<td>0.82 (0.01)</td>
<td>0.71 (0.37)</td>
<td>0.025</td>
</tr>
<tr>
<td>Insulin pump treatment (%)</td>
<td>20.0</td>
<td>20.6</td>
<td>21.8</td>
<td>ns</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.97 (0.01)</td>
<td>8.24 (0.07)</td>
<td>8.3 (0.18)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Smoking (Cig/d)</td>
<td>2.3 (0.04)</td>
<td>4.2 (0.30)</td>
<td>3.9 (1.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RR Systolic (mmHg)</td>
<td>119.5 (0.09)</td>
<td>123.0 (0.51)</td>
<td>126.6 (2.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>70.2 (0.06)</td>
<td>72.2 (0.3)</td>
<td>74.2 (1.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Most recent BMI-SDS *</td>
<td>0.65 (0.06)</td>
<td>0.75 (0.04)</td>
<td>0.71 (0.12)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

**Dyslipidemia**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Nephropathy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chol total (mg/dl)</td>
<td>183.4 (0.29)</td>
<td>197.1 (1.7)</td>
<td>203.3 (5.7)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Chol LDL (mg/dl)</td>
<td>99.9 (0.28)</td>
<td>106.3 (1.5)</td>
<td>111.4 (7.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>119.4 (0.62)</td>
<td>139.8 (3.6)</td>
<td>144.3 (11.2)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

**Antihypertensives **

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Nephropathy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitors (%)</td>
<td>4.9 (0.13)</td>
<td>14.7 (1.1)</td>
<td>34.6 (5.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Ca-antagonists (%)</td>
<td>1.0 (0.06)</td>
<td>4.7 (0.8)</td>
<td>21.8 (4.7)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>1.9 (0.01)</td>
<td>7.0 (0.8)</td>
<td>30.7 (5.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>2.6 (0.01)</td>
<td>7.6 (0.9)</td>
<td>25.6 (4.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ARBs (Sartane) (%)</td>
<td>0.8 (0.05)</td>
<td>3.1 (0.6)</td>
<td>11.6 (3.6)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Values represent mean values (SE)

* According to actual normative data of the German working group of obesity (AGA)

** Alone or in combination

*** Statistics normal versus nephropathy, Kruskal-Wallis test.
Table 2—Logistic regression analysis of risk factors for microalbuminuria and macroalbuminuria (without ESRD). Analysis of maximum likelihood estimates and stepwise selection of parameters. Risk factors were calculated as continuous variables for microalbuminuria and dichotomous factors for macroalbuminuria.

<table>
<thead>
<tr>
<th></th>
<th>Microalbuminuria</th>
<th></th>
<th>Macroalbuminuria</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value</td>
<td>OR</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>&lt; 0.0001</td>
<td>1.033</td>
<td>1.027-1.039</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>&lt; 0.0001</td>
<td>1.011</td>
<td>1.006-1.017</td>
<td>0.28</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.681</td>
<td>0.969</td>
<td>0.835-1.125</td>
<td>0.047</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt; 0.0001</td>
<td>1.13</td>
<td>1.086-1.181</td>
<td>0.0039</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>0.033</td>
<td>1.008</td>
<td>1.001-1.016</td>
<td>nd</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.015</td>
<td>1.014</td>
<td>1.003-1.026</td>
<td>nd</td>
</tr>
<tr>
<td>Hypertension</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>0.018</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>LDL-chol</td>
<td>0.0074</td>
<td>1.003</td>
<td>1.001-1.005</td>
<td>nd</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 0.0001</td>
<td>1.003</td>
<td>1.002-1.003</td>
<td>nd</td>
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<tr>
<td>Dyslipidemia</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>0.0061</td>
</tr>
</tbody>
</table>

Odds ratio (OR) and 95% confidence interval (CI), not done (nd)
Figure Legends

Figure 1:
Age at last visit (1A) and age at time of diagnosis (1B) of 27,805 patients with type 1 diabetes included into nephropathy evaluation.

Figure 2:
Survival free period of microalbuminuria (solid) and macroalbuminuria (hatched) in patients with type 1 diabetes. Graphs show cumulative incidence and 95% confidence interval (CI) of microalbuminuria and macroalbuminuria obtained by Kaplan-Meier hazard analysis.

Figure 3:
Influence of HBA1c on development of microalbuminuria (Fig. 3A) and macroalbuminuria (3B) over time (Kaplan-Meier analysis). Graphs show cumulative incidence of patients with HbA1c above (solid) and equal or lower than 7.5% (hatched).
Figure 1

A

B

Age at diagnosis [yrs]

Patients (n)

Age at last visit [yrs]

Patients (n)
Figure 2

![Graph showing percentage without albuminuria vs. diabetes duration](image)

- **Macroalbuminuria & ESRD**
- **Microalbuminuria**

% without albuminuria

Diabetes duration (years)

N = 12200 7825 3685 1331 830 622 528 315 221 248
Figure 3

A

% without albuminuria

- HbA1c ≤ 7.5%
- HbA1c > 7.5%
- P < 0.0001

Diabetes duration (years)

N = 12200 7825 3685 1331 830 622 528 315 221 248