Diabetic Nephropathy in 27,805 Children, Adolescents, and Adults With Type 1 Diabetes

Effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex

KLEMENS RAILE, MD[1]
ANGELA GALLER, MD[2]
SABINE HOFER, MD[3]
ANTJE HERBST, MD[4]
DESIREE DUNSTHEIMER, MD[5]
PETRA BUSCH, MD[6]
REINHARD W. HOLL, MD[7]

OBJECTIVE — To give an up-to-date profile of nephropathy and the 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 — A total of 27,805 patients from the nationwide, prospective German Diabetes Documentation System survey were included in the present analysis. Inclusion criteria were at least two documented urine analyses with identical classification. Urine analyses, treatment regimens, diabetes complications, and risk factors were recorded prospectively. Baseline characteristics were age at diagnosis 9.94 years (median [interquartile range 5.8–14.3]), age at last visit 16.34 years (12.5–22.2), and follow-up time 2.5 years (0.43–5.3). Cumulative incidence of nephropathy was tested by Kaplan-Meier analysis and 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% CI 22.3–28.3) had microalbuminuria and 9.4% (8.3–11.4) had macroalbuminuria or ESRD. Risk factors for microalbuminuria were diabetes duration (odds ratio 1.033, $P < 0.0001$), A1C (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 sex was associated with the development of macroalbuminuria.

CONCLUSIONS — Diabetes duration, A1C, dyslipidemia, blood pressure, and male sex were identified as risk factors for nephropathy. Therefore, besides the best possible metabolic control, early diagnosis and prompt treatment of dyslipidemia and hypertension is mandatory in patients with type 1 diabetes.

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From the [1]Department of Pediatric Endocrinology and Diabetes, Charité Children's Hospital, Berlin, Germany; the [2]Department of Pediatric Endocrinology and Diabetes, University Hospital for Children and Adolescents, Leipzig, Germany; the [3]Department of Pediatrics, Medical University of Innsbruck, Innsbruck, Austria; the [4]Department of Pediatric Diabetology, Children's Hospital, Leverkusen, Germany; the [5]Children's Hospital, Klinikum Augsburg, Ausburg, Germany; the [6]Department of Internal Medicine II, SLK-Kliniken Heilbronn, Heilbronn, Germany; and the [7]Department of Epidemiology, University of Ulm, Ulm, Germany.

Address correspondence and reprint requests to Klemens Raile, MD, Department of Pediatric Endocrinology and Diabetes, Charité Children's Hospital, Augustenburger Platz 1, 13353 Berlin, Germany. E-mail: klemens.raile@charite.de.

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Abbreviations: AER, albumin excretion rate; DCCT, Diabetes Control and Complications Trial; DPV, German Diabetes Documentation System; ESRD, end-stage renal disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Micro- and macroalbuminuria are important markers for early and progressive diabetic kidney disease. Patients with type 1 diabetes face a 20–50% probability of developing 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 currently albumin excretion rate (AER) remains the best available noninvasive predictor 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 the development of diabetic nephropathy (9). Moreover, the DCCT follow-up Epidemiology of Diabetes Interventions and Complications study has demonstrated a persistent delay of progression of diabetic nephropathy 7–8 years after the end of the DCCT, in the previously intensively treated patients (10). Next to A1C, presence of retinopathy, smoking, dyslipidemia, hypertension, and male sex have previously been reported as risk factors for progression toward 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 childhood-onset diabetes, young age at diagnosis and a longer prepubertal run seem to delay the time until the development of microalbuminuria, a phenomenon that is not yet understood (17,18).

The aim of this study was first to analyze the prevalence of nephropathy

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

		Nephropathy		
	Normal	Microalbuminuria	Macroalbuminuria/ ESRD	*P**
n	26,644	919	52/229	
Sex, male (%)	52.6	52.1	58.0	NS
Age at last visit (years)	21.1 ± 0.09	28.7 ± 0.64	37.2 ± 1.2	<0.0001
Diabetes duration (years)	8.3 ± 0.054	12.6 ± 0.39	20.1 ± 0.86	<0.0001
Age at onset (years)	12.9 ± 0.07	16.1 ± 0.45	17.2 ± 0.78	<0.0001
Insulin dose (IE · kg^{-1} · day^{-1})	0.80 ± 0.002	0.82 ± 0.01	0.71 ± 0.37	0.025
Insulin pump treatment (%)	20.0	20.6	21.8	NS
A1C (%)	7.97 ± 0.01	8.24 ± 0.07	8.3 ± 0.18	0.0019
Smoking (cigarettes/day)	2.3 ± 0.04	4.2 ± 0.30	3.9 ± 1.0	<0.0001
Blood pressure				
Systolic (mmHg)	119.5 ± 0.09	123.0 ± 0.51	126.6 ± 2.3	<0.0001
Diastolic (mmHg)	70.2 ± 0.06	72.2 ± 0.3	74.2 ± 1.3	<0.0001
Most recent BMI-SDS†	0.65 ± 0.06	0.75 ± 0.04	0.71 ± 0.12	0.024
Dyslipidemia				
Total cholesterol (mg/dl)	183.4 ± 0.29	197.1 ± 1.7	203.3 ± 5.7	<0.0001
LDL cholesterol (mg/dl)	99.9 ± 0.28	106.3 ± 1.5	111.4 ± 7.1	<0.0001
Triglycerides (mg/dl)	119.4 ± 0.62	139.8 ± 3.6	144.3 ± 11.2	<0.0001
Antihypertensive medications‡				
ACE inhibitors (%)	4.9 ± 0.13	14.7 ± 1.1	34.6 ± 5.4	<0.0001
Ca antagonists (%)	1.0 ± 0.06	4.7 ± 0.8	21.8 ± 4.7	<0.0001
Diuretics (%)	1.9 ± 0.01	7.0 ± 0.8	30.7 ± 5.2	<0.0001
β-blockers (%)	2.6 ± 0.01	7.6 ± 0.9	25.6 ± 4.9	<0.0001
Angiotensin receptor blockers (Sartane) (%)	0.8 ± 0.05	3.1 ± 0.6	11.6 ± 3.6	<0.0001

Data are means ± SE. *Statistics normal versus nephropathy, Kruskal-Wallis test. †According to actual normative data of the German Working Group of Obesity. ‡Alone or in combination. NS, not significant.

in a nationwide, prospective survey including children, adolescents, and adults with type 1 diabetes from Germany and Austria. Second, 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 are listed in the online appendix (available at http://dx.doi.org/10.2337/dc07-0282). 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 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, sex, blood pressure, A1C, dyslipidemia, cumulative A1C, and smoking.

Assessment of nephropathy

Screening for microalbuminuria was performed by the following methods: *1*) measurement of the urine albumin-to-creatinine ratio (UAC) 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 the follow-up period. Within the most recent year, albuminuria was determined by the UAC ratio in 12.1%, AER (24 h) in 31.7%, and albumin concentration from a timed overnight collection in 56.2% of subjects. Thresholds were AER ≥20 μg/min or a UAC ≥2.5 mg/mmol, according to guidelines of American Diabetes Association (21). Macroalbuminuria was defined as AER ≥200 μg/min or a UAC ≥35 mg/mmol. Albumin and creatinine were 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 the Kaplan-Meier survival analysis to adequately reflect prevalence of severe nephropathy but were excluded from regression analysis for macroalbuminuria-associated covariates.

Risk factors for diabetic kidney disease

A1C. Glycemic control was assessed as mean A1C during the follow-up period. Single-center A1C methods were standardized according to the DCCT reference range of 4.05–6.05% (22).

Hypertension. Systolic and diastolic blood pressure were 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. Cutoffs were for total cholesterol >200 mg/dl, LDL cholesterol >160 mg/dl, and triglycerides >150 mg/dl. In logistic regression analysis for microalbuminuria, triglycerides, and HDL and LDL cholesterol were treated as independent, continuous variables, whereas for macroalbuminuria, dyslipidemia was treated as a dichotomous variable.

Smoking. Subjects' smoking habits were asked 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. Lipid-lowering drugs used were statins, fibrates, or cholesterol absorption inhibitors such as ezetimibe. Treatment with antihypertensive drugs were classified and docu-

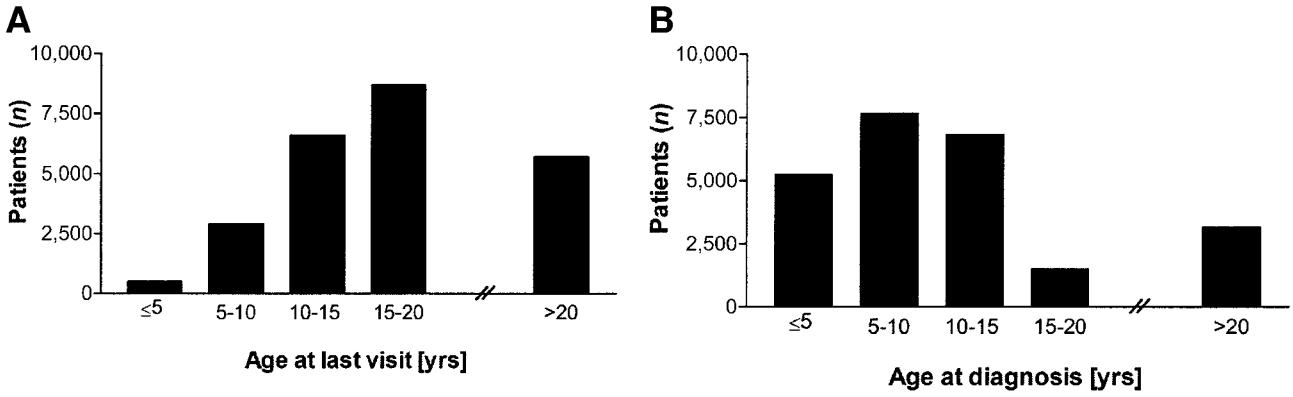

Figure 1—*Age at last visit* (A) *and age at time of diagnosis* (B) *of 27,805 patients with type 1 diabetes included into nephropathy evaluation.*

mented as ACE inhibitors, angiotensine receptor blockers, β-blockers, diuretics, and calcium channel blockers. Pharmacotherapy with these respective drugs was documented in a qualitative fashion.

Statistical analysis

The SAS 9.1 statistical software package was used for data evaluation and statistical analysis. In detail, the 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 the nonparametric Mann-Whitney *U* test (Table 1). The odds ratio (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 ± SE, where appropriate.

RESULTS

Cohort characteristics

The study cohort was analyzed in February 2007 from 262 diabetes centers in Germany and Austria, with a total number of 49,027 patients with type 1 diabetes being continuously followed in the DPV. At the time of analysis, 27,805 patients had at least two documented urine tests with clear results 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 the DPV, as A1C (mean; included 7.99 vs. all 7.92%), male sex (52.5 vs. 51.9%), age (21.1 vs. 21.4 years), diabetes duration (8.3 vs. 7.8 years), and age at diabetes onset (12.9 vs. 13.6 years) were largely comparable. The following were the characteristics of the analyzed cohort: follow-up time (median [interquartile range]) 2.5 years (0.5–5.3), follow-up visits 12.0 (3.0–26.0), A1C determinations 9.0 (9–21), and blood pressure measurements 12 (3.0–26.0). Age at the most recent visit (Fig. 1*A*) and age at diagnose (Fig. 1*B*) 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 were found in 1,200 patients (4.3%). Among the latter group, 281 of 1,200 (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 only macroalbuminuric and 229 proceeded toward ESRD.

Comparing patients with normoalbuminuria and micro- or macroalbuminuria, the variables A1C, systolic and diastolic blood pressure, tobacco consumption, and serum lipids, including cholesterol, LDL cholesterol, and triglycerides, were found to be higher in patients with increased albumin excretion (Table 1). But these changes were parallel with increasing age, changed insulin treatment regimens, and had longer diabetes duration, and therefore these findings were only noticed in a descriptive fashion. Treatment with antihypertensive drugs increased with severity of nephropathy, but it still was unacceptably low in patients with micro- or macroalbuminuria (Table 1).

Survival analysis of micro- and macroalbuminuria

Kaplan-Meier analysis revealed that after median diabetes duration of 40 years, 25.4% (95% CI 22.3–28.3) of patients had microalbuminuria and 9.4% (8.3–11.4) had macroalbuminuria or ESRD

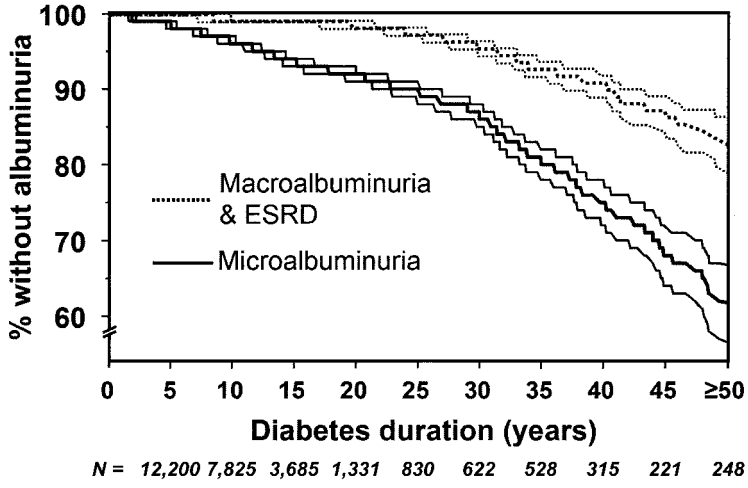

Figure 2—*Survival free period of microalbuminuria (solid lines) and macroalbuminuria (hatched lines) in patients with type 1 diabetes. Graphs show cumulative incidence and 95% CI of microalbuminuria and macroalbuminuria obtained by Kaplan-Meier hazard analysis.*

(Fig. 2). To describe the long-term influence of A1C on nephropathy, patients were stratified into two groups: one with A1C levels above and one with A1C levels below 7.5%. The group with with A1C levels >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 with levels <7.5% (Figs. 3*A* and *B*). Differences between groups became evident after diabetes duration of ~10 years for microalbuminuria and 20 years for macroalbuminuria.

Nephropathy and age, sex, smoking, and onset of diabetes

Logistic regression analysis with stepwise selection of parameters identified diabetes duration, dyslipidemia, and mean A1C as significant risk factors for development of microalbuminuria. When blood pressure and lipid levels were analyzed as continuous variables, and not as dichotomous cutoff levels, systolic and diastolic blood pressure, but also triglyceride and LDL cholesterol concentration, became independent and significant risk factors for the development of microalbuminuria. In the relatively small number of patients with macroalbuminuria, diabetes duration, A1C, male sex, and dyslipidemia were associated with the development of overt nephropathy. Also, young age at diagnosis reduced the risk of microalbuminuria, when adjusted for diabetes duration and other independent covariates (Table 2). Smoking and sex were included in a stepwise selection of potential risk factors, but only male sex was associated with the development of macroalbuminuria.

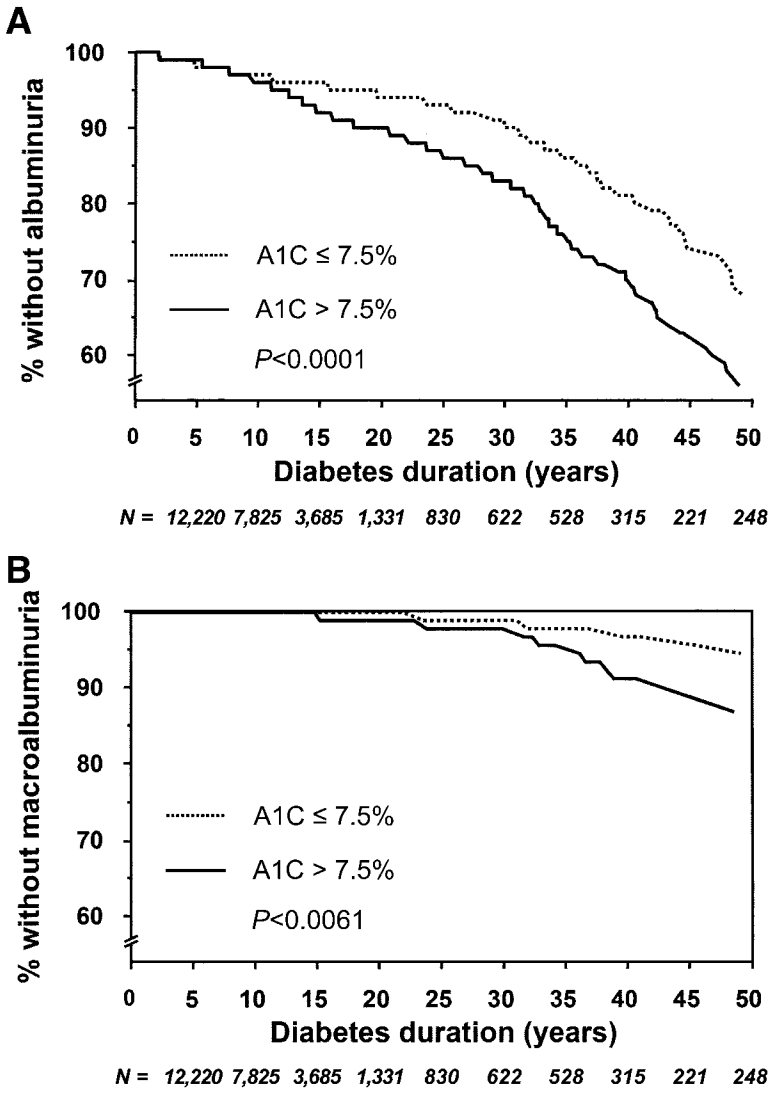

Figure 3—*Influence of A1C on development of microalbuminuria* (A) *and macroalbuminuria* (B) *over time (Kaplan-Meier analysis). Graphs show cumulative incidence of patients with A1C above (solid lines) and ≤7.5% (hatched lines).*

CONCLUSIONS — We analyzed the 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 duration, calculated prevalence was 25.4% for persistent microalbuminuria but <10% for macroalbuminuria or ESRD. This is a lower rate of nephropathy than reported earlier from cohorts followed in Denmark, England, and western Australia, with similar age of patients (11,17,24). The most prominent difference in our study was a lower A1C level compared with 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 A1C, serum lipids, in-detail LDL cholesterol and triglycerides, and systolic and diastolic blood pressure as well as with older age at diagnosis. Macroalbuminuria, documented in a much smaller number of patients, was linked to A1C, dyslipidemia, and male sex.

Increased A1C 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 (11,13,14,17). The DCCT and the follow-up Epidemiology of Diabetes Interventions and Complications study clearly demonstrate that previous intensive treatment of diabetes with near-normal glycemia has an extended benefit in delaying the development and progression of diabetic nephropathy (9, 10). By Kaplan-Meier analysis, we found that a cumulative A1C of >7.5% significantly raised the probability of micro- and macroalbuminuria. This effect became evident after diabetes duration of >10 years for microalbuminuria and >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. Hyperten-

Table 2—*Logistic regression analysis of risk factors for microalbuminuria and macroalbuminuria (without ESRD)*

	Microalbuminuria		Macroalbuminuria	
	P value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)
Diabetes duration	<0.0001	1.033 (1.027–1.039)	<0.0001	1.054 (1.036–1.073)
Age at onset (years)	<0.0001	1.011 (1.006–1.017)	0.28	0.989 (0.969–1.009)
Male sex	0.681	0.969 (0.835–1.125)	0.047	1.290 (1.003–1.658)
A1C	<0.0001	1.13 (1.086–1.181)	0.0039	1.235 (1.070–1.426)
Blood pressure				
Systolic	0.033	1.008 (1.001–1.016)	ND	ND
Diastolic	0.015	1.014 (1.003–1.026)	ND	ND
Hypertension	ND	ND	0.018	0.414 (0.199–0.860)
Lipids				
LDL cholesterol	0.0074	1.003 (1.001–1.005)	ND	ND
Triglycerides	<0.0001	1.003 (1.002–1.003)	ND	ND
Dyslipidemia	ND	ND	0.0061	1.727 (0.887–3.361)

Analysis of maximum likelihood estimates and stepwise selection of parameters. Risk factors were calculated as continuous variables for microalbuminuria and dichotomous factors for macroalbuminuria. ND, not done.

sion, 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 the cause or result of nephropathy, hypertension should strictly be treated also in pediatric and adolescent patients (25).

Dyslipidemia, as the strongest single factor for elevated LDL cholesterol, is associated with progression of diabetic kidney disease (12,26). We found that both LDL cholesterol and triglycerides are independently associated with microalbuminuria. Furthermore, association between serum advanced glycation end products and increased serum cholesterol imply involvement of lipids in the formation of advanced glycation end products and, by this way, in renal disease (27).

The 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 (28); however, it has recently been controversially discussed whether smoking is a risk factor for development or progression of diabetic kidney disease (13,29,30). We did not find that smoking increased the 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).

Sex influence on nephropathy has been found to be age dependent. In adolescents, female sex increases the risk of microalbuminuria (14,17), while in adults and in terms of advanced nephropathy, men are at higher risk to develop renal disease, if data were adjusted to social class, A1C, smoking status, and blood pressure (11,16). We found no link between sex and microalbuminuria but higher risk for macroalbuminuria in male subjects.

Several studies have indicated that prepubertal duration of diabetes delays the onset of diabetic nephropathy. In our study, microalbuminuria was delayed by very early onset of diabetes and confirmed these previous prospective studies (14,31,32). 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 lower rate (33).

In conclusion, diabetes duration, long-term metabolic control (A1C), dyslipidemia, and male sex have been identified as independent risk factors for the development of nephropathy in this large cohort. We conclude from our data that diabetes care must continue to focus on long-term metabolic control as well as on reduction of additional risk factors like dyslipidemia and blood pressure.

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We kindly acknowledge each of the 262 participating diabetes centers in Germany and Austria. These centers are listed in the online appendix.

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