Signs of Nephropathy May Occur Early in Young Adults With Diabetes Despite Modern Diabetes Management

Results from the nationwide population-based Diabetes Incidence Study in Sweden (DISS)

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OBJECTIVE — To estimate the occurrence of early-onset renal involvement in a nationwide population-based cohort of young adults with diabetes in Sweden and relate the findings to glycemic control, type of diabetes, sex, smoking, and blood pressure.

RESEARCH DESIGN AND METHODS — The Diabetes Incidence Study in Sweden aims to register all incident cases of diabetes in the age-group 15–34 years. In 1987–1988, 806 patients were reported and invited to participate in a follow-up study focusing on microvascular complications. Of them, 469 subjects participated. The assessment was based on questionnaires ($n = 469$), blood samples ($n = 424$), urine samples ($n = 251$) and, when appropriate, medical records ($n = 186$).

RESULTS — During the follow-up time, median 9 years (range 6–12), 31 of 469 patients (6.6%) with incipient or overt diabetic nephropathy (i.e., micro- or macroalbuminuria) were found, 24 of 426 (5.6%) in type 1 and 7 of 43 (16%) in type 2 diabetic subjects ($P = 0.016$). Additionally, 24 of 31 patients (77%) had microalbuminuria and 7 (23%) had macroalbuminuria, which mainly occurred in patients with type 2 diabetes. In a Cox regression analysis, high mean HbA_{1c} during the follow-up period and high blood pressure at follow-up increased the risk of developing signs of nephropathy ($P = 0.020$ and $P = 0.003$, respectively). Compared with patients with type 1 diabetes, those with type 2 diabetes tended to have an increased risk of renal involvement ($P = 0.054$) when adjusting for sex, tobacco use, glycemic control, and blood pressure.

CONCLUSIONS — Despite modern treatment and self-monitoring of blood glucose, young adult patients with diabetes may still develop renal involvement during the first 10 years of diabetes duration. Inadequate HbA_{1c}, high blood pressure, and type 2 diabetes appear to be risk markers for early occurrence of diabetic nephropathy.

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Overt diabetic nephropathy, i.e., macroalbuminuria, is a serious complication of diabetes and is linked to a high risk of developing renal failure and cardiovascular disease (1). Persistent microalbuminuria, i.e., incipient nephropathy, can also predict overt diabetic nephropathy and cardiovascular complications (2,3). Improved long-term glycemic control has reduced the risk of developing diabetic nephropathy (4,5). The cumulative incidence of overt diabetic nephropathy after 25–30 years has been reported to be nearly 30% in type 1 diabetes (6). In type 2 diabetes, the incidence and prevalence of nephropathy is more uncertain, but in a cross-sectional study 30% of patients had microalbuminuria and 17% had macroalbuminuria after ~10 years of diabetes duration (7).

Hyperglycemia is necessary, but other factors, e.g., hypertension, smoking, and genetic susceptibility, contribute to the development of diabetic nephropathy (8–10). Besides intensified glycemic control, effective blood pressure control is of great importance to delay the development and progression of diabetic nephropathy (11). Accumulating evidence indicates that treatment with ACE inhibitor or angiotensin II receptor blockers have specific beneficial effects (12,13).

The relationship between hyperglycemia and microvascular complications is the basis for the recommendations to optimize glycemic control. Multiple insulin injections or continuous subcutaneous insulin infusion (CSII) in combination with self-monitoring of blood glucose are currently part of the standard management for type 1 diabetes in many coun-

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Abbreviations: CSII, continuous subcutaneous insulin infusion; DISS, Diabetes Incidence Study in Sweden.

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

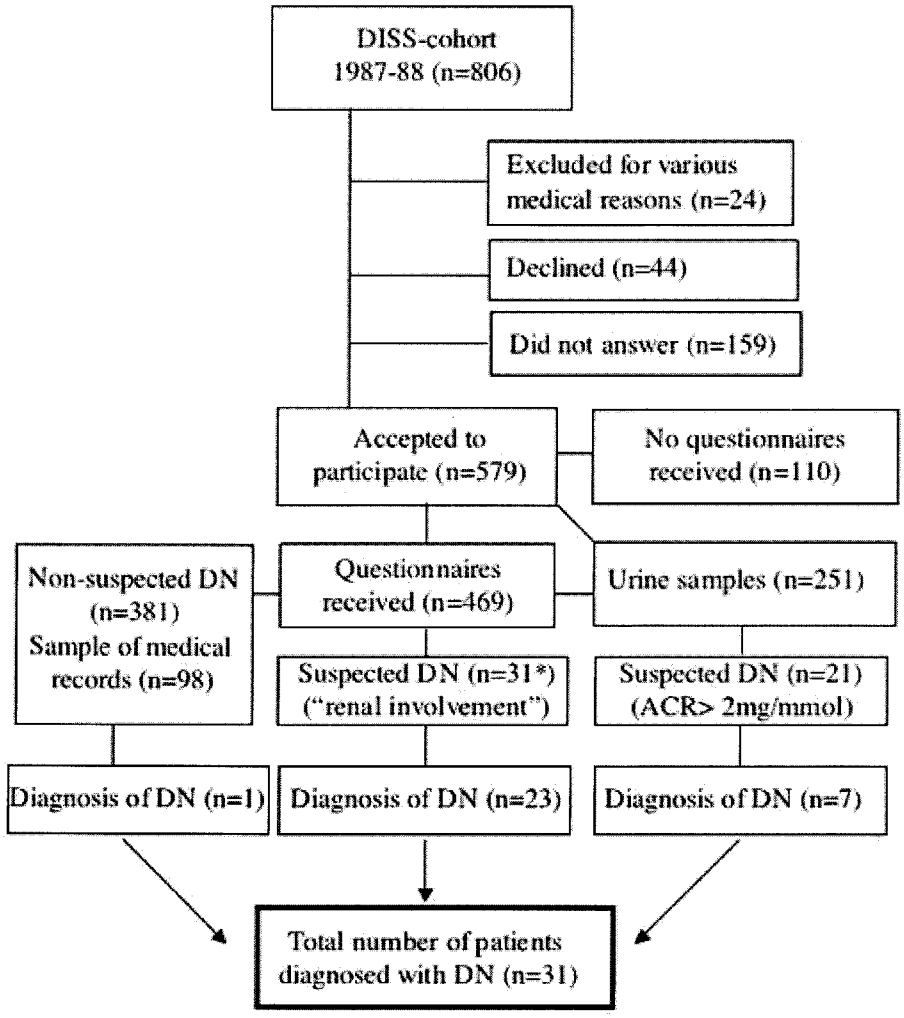

Figure 1—*Flow chart for recruitment of participants and identification of subjects with renal involvement, i.e., micro- or macroalbuminuria, in the study. The questionnaires and urine samples were used as a first step to identify patients suspected for diabetic nephropathy (DN). *Among those 31 patients, 8 were considered not to have DN (2 patients with glomerulonephritis, 1 with pyelonephritis, and 5 who did not fulfill the criteria for DN). ACR, albumin-to-creatinine ratio.*

tries. This therapy has been adopted in Sweden for >15 years (14). Therefore, the occurrence of diabetes complications has been expected to decline during the last decade, and this has also been found in some studies (5,15).

The aim of this study was to estimate the occurrence of early-onset (within ~10 years of diabetes duration) renal involvement in a nationwide population-based cohort of young adults with diabetes diagnosed at age 15–34 years, treated after the implementation of the Diabetes Control and Complications Trial (4) and the Stockholm studies (14). We also wanted to study whether the occurrence of micro- or macroalbuminuria was affected not only by the degree of glycemic control but also by other factors such as type of diabetes, sex, smoking, and blood pressure.

RESEARCH DESIGN AND METHODS

Patients, questionnaires, and blood and urine samples

Since 1983, the Diabetes Incidence Study in Sweden (DISS) has aimed to register all newly diagnosed cases of diabetes, except gestational diabetes, in the age-group 15–34 years. The ascertainment rate has been ~85% (16). Patients who were reported to the DISS during the years 1987 and 1988 were tested for islet antibodies at diagnosis. Among the 806 patients of the 1987–1988 cohort, 24 patients were excluded for various medical reasons (3 patients had gestational diabetes, 3 had secondary diabetes, 4 did not have diabetes, 2 had contagious blood samples, 3 were dead, and 9 had emigrated). In 1994, the remaining 782 patients were invited to participate in a follow-up study on diabetes complications, of whom 579 (74%) accepted. A questionnaire was sent to their treating physicians who between 1994 and 1999 delivered clinical data, including height, weight, tobacco use, type of diabetes (clinical classification), current medication, present blood pressure, all HbA_{1c} values since diagnosis, and clinical diagnosis of micro- and macrovascular complications. The patients were also asked to provide a random blood sample to our central laboratory for measurements of C-peptide and HbA_{1c} and, in addition, two consecutive overnight urine collections for measurement of urinary albumin and creatinine to screen for suspected renal involvement. The median follow-up time from the questionnaires was 9 years (range 6–12).

Among the 579 patients who agreed to follow-up, questionnaires were received for 469 patients, who formed the study cohort. Among these 469 patients, 424 delivered a blood sample and 251 provided at least one urine sample. If a patient had delivered a urine or blood sample but no questionnaire, a questionnaire was filled in afterward by one of the investigators based on information in medical records. There were 44 patients who declined follow-up and 159 who did not respond to the invitation. Hence, a total of 469 patients with diabetes comprised the study population. The process of subject recruitment is outlined in Fig. 1. The study was approved as a multicenter investigation by the Ethics Committee at the University of Lund, Sweden.

Diabetes classification

The clinical classification of type 1, type 2, secondary, or unclassifiable diabetes, both at onset and at follow-up, was made by the reporting physician according to World Health Organization criteria (17) without access to the results of C-peptide or islet antibody measurements. As a clinical classification is uncertain (18,19), we used the results of islet antibody analyses, at diagnosis in 1987–1988, to make a more accurate classification (20). Patients reported as having type 1 diabetes at fol-

low-up and patients clinically considered as having type 2 or unclassifiable diabetes but displaying any islet antibody at diagnosis were all classified as having type 1 diabetes ($n = 426$). Patients reported as type 2 or unclassifiable diabetes by the treating physician and lacking islet antibodies at diagnosis were all considered as having type 2 diabetes ($n = 43$) (21). C-peptide was not considered in this reclassification. A reclassification from type 2 to type 1 diabetes was thus made in 15 of 50 (30%) subjects clinically diagnosed with type 2 diabetes. Among the 14 patients with clinically unclassifiable diabetes, 6 were classified as having type 1 and 8 as having type 2 diabetes.

Nephropathy

In this study, the term diabetic nephropathy refers to both incipient nephropathy (persistent microalbuminuria) and overt nephropathy (macroalbuminuria) (22). The identification of subjects with diabetic nephropathy was performed in two steps. First, all subjects who were in any way suspected of having renal involvement were identified by either clinical information in the questionnaires or, alternatively, a urinary albumin-to-creatinine ratio >2 mg/mmol in any of the study urine samples. Patients were suspected of having diabetic nephropathy from the questionnaires when reported to have signs of renal involvement (i.e., micro- or macroalbuminuria, elevated serum creatinine, or renal replacement therapy). Second, the medical records, including laboratory reports, of all subjects with suspected diabetic nephropathy ($n = 52$), as well as those lacking complete information in the questionnaires ($n = 36$), were collected. They were evaluated in detail up to the time when the questionnaire was filled in or, alternatively, if there was no questionnaire, until 31 December 1999. To confirm diabetic nephropathy from data in medical records and laboratory reports, including the study urine samples, we used the following criteria: at least two of three consecutive urine samples displaying an albumin excretion rate 20–199 μg/min (timed collections), an albumin concentration 30–299 mg/l (spot samples) for microalbuminuria, and >200 μg/min or >300 mg/l for macroalbuminuria (23). If any renal disease other than diabetic nephropathy was suspected because of results from urine analyses (hematuria or leukocyturia), rapid progression of albuminuria, rapid decline in glomerular filtration rate, or findings in kidney biopsies, the patient was not considered to have diabetic nephropathy ($n = 3$) (Fig. 1). Figure 1 shows that of the 31 patients with confirmed diabetic nephropathy, 23 were initially identified via the questionnaires and 7 via the urine screening alone. One additional case was identified in a sample ($n = 98$) of patients without suspected nephropathy ($n = 381$). Onset of diabetic nephropathy was defined as the day when the first of two consecutive urine samples verifying the diagnosis of micro- or macroalbuminuria was collected.

Retinopathy

Data on retinal status were available in 424 patients and are reported in detail in a separate 10-year follow-up study on this DISS cohort (20). Retinopathy was graded according to the method suggested by Klein et al. (24).

Neuropathy was reported as present or absent in the questionnaires according to clinical examination. Tobacco use was defined as current or previous daily use. Systolic (SBP) and diastolic blood pressures (DBP) at follow-up were reported in the questionnaires. The mean arterial pressure (MAP) was calculated as follows: $MAP = DBP + [(SBP - DBP)/3]$.

Blood and urine chemistry

HbA_{1c} was measured using ion-chromatography at the local hospital laboratories (25). The mean value during the entire follow-up period was estimated for each patient. The HbA_{1c} values were weighted with adjustments for the time between the measurements (26). The number of HbA_{1c} measurements during the follow-up period was 16 ± 8 (range 1–43). Random plasma C-peptide was measured in blood samples at follow-up by a radioimmunoassay (27), and urinary albumin was analyzed with an enzyme-linked immunosorbent assay (28). Islet antibodies were measured in serum samples obtained at diabetes diagnosis. Islet cell antibodies were determined by a prolonged immunofluorescence assay as previously described (29). GAD antibodies were measured by a radioligand binding assay using in vitro–translated ^{35}S-methionine–labeled GAD65 (30).

Statistical methods

When analyzing differences in variables between groups, the Student's two-tailed *t* test or a χ^2 test was used. For variables not normally distributed, Mann-Whitney *U* nonparametric test was used. Mean HbA_{1c} was calculated using the area under the curve of HbA_{1c} over time to compensate for the occasionally irregular intervals between the measurements (26). Data are presented as mean ± SD or as indicated. The Kaplan-Meier analysis was used to calculate the probability of nephropathy-free survival, and differences between groups were tested by log-rank test. A Cox proportional hazard analysis was used to assess the influence of different potential confounding variables on the occurrence of diabetic nephropathy. A P value <0.05 was considered statistically significant. Results were given with 95% CI. SPSS 10.0 Macintosh version (The Software MacKiev Company, Cupertino, CA) was used to analyze data.

RESULTS — Using data from questionnaires and study urine samples, we identified, in total, 30 patients who fulfilled the criteria for diabetic nephropathy, i.e., micro- or macroalbuminuria. To validate the case finding of renal involvement, 105 patients were randomly selected among patients with a completed questionnaire but without any suspicion of nephropathy ($n = 381$). Medical records were received from 98 of these patients. Only one patient fulfilled the criteria for nephropathy at the time the questionnaire was completed (1.0%). This indicates a reasonable ascertainment of the case-finding procedure. Thus, altogether we found 31 patients with renal involvement ($n = 31$ of 469, 6.6%) during the follow-up period.

There were no differences between patients who accepted follow-up ($n = 579$) and those who completed their questionnaire ($n = 469$) with regard to clinical characteristics (sex, age at onset, and reported type of diabetes). When comparing the participants in the follow-up study ($n = 469$) with all the remaining patients in the DISS cohorts of 1987 and 1988 ($n = 337$), the participants were more often reported as having type 1 diabetes (79 vs. 64%, $P < 0.001$). Among nonparticipants ($n = 203$), 77 patients gave their consent to collect medical records and clinical data. Medical records were retrieved from 63 of these patients, 6 (9.5%) of whom fulfilled the crite-

Table 1—*Clinical and biochemical characteristics at follow-up among patients with and without signs of diabetic nephropathy (DN), i.e., micro- or macroalbuminuria, in the DISS 1987–1988 cohort*

	DN	No DN	*P*
n	31	438	
Male	22 (71)	262 (60)	0.15
Female	9 (29)	179 (40)	
Age at diabetes onset (years)	25.9 ± 6.7 (15–34)	24.7 ± 3.4 (15–34)	0.30
BMI (kg/m^2) (n = 446)	25.9 ± 6.7 (16.4–38.5)	24.7 ± 5.8 (18.0–38.6)	0.011
Any tobacco use (n = 454)	16 (53)	205 (40)	0.37
Type of diabetes*			
Type 1 diabetes	24 (77)	402 (92)	0.016
Type 2 diabetes	7 (23)	36 (8)	
Mean HbA_{1c} (%) (n = 428)	8.2 ± 1.6 (5.9–11.2)	7.2 ± 1.4 (3.7–11.7)	0.001
C-peptide > 0.1 nmol/l (n = 469)	11 (36)	152 (35)	0.54
Islet antibodies (n = 361)	15 (62)	281 (83)	0.016
Mean arterial blood pressure (mmHg) (n = 453)	98 ± 13 (78–120)	91 ± 8 (68–121)	<0.001
Antihypertensive treatment (n = 460)	8 (26)	15 (3.4)	<0.001
Any retinopathy (n = 424)	14 (45)	143 (36)	0.34
Proliferative retinopathy	2 (6)	2 (0.5)	0.028
Macular edema	3 (10)	15 (4)	0.14
Peripheral neuropathy (n = 449)	3 (10)	13 (3)	0.076
Autonomic neuropathy (n = 461)	5 (16)	12 (3)	0.003

Data are means ± SD (range) or *n* (%). *n* = numbers of patients with information on each separate variable. *Type of diabetes after reclassification, see RESEARCH DESIGN AND METHODS.

ria for incipient or overt diabetic nephropathy. Among these 63 patients, the time to follow-up was somewhat longer and type 2 diabetes was more frequent (P < 0.001) compared with the participants. The occurrence of diabetic nephropathy, however, was not significantly increased in these patients compared with the participants (9.5 vs. 6.6%, P = 0.55). Participating patients with type 2 diabetes were more often women (P = 0.039) and tobacco users (P = 0.016), and they were older at diagnosis of diabetes (P < 0.001) compared with patients with type 1 diabetes.

Development of nephropathy

Clinical and biochemical data on patients with and without diabetic nephropathy are summarized in Table 1. Of 469 (6.6%) patients, 31 developed micro- or macroalbuminuria during the follow-up period. This was more frequent among patients with type 2 diabetes than those with type 1 diabetes (7/43 [16%] vs. 24/426 [5.6%], P = 0.016). Most of the patients with diabetic nephropathy (24 [77%]) had microalbuminuria, but 7 (23%) had macroalbuminuria (4/24 [17%] with type 1 and 3/7 [42%] with type 2 diabetes, P = 0.017). Only one of the patients with diabetic nephropathy had elevated serum creatinine and had actually been accepted for kidney transplantation at the time of follow-up. The median time to the diagnosis of diabetic nephropathy was 7.9 years (range 0–12) from onset of diabetes. There were no significant differences in sex, age at onset of diabetes, or tobacco use between patients with or without diabetic nephropathy. Patients with diabetic nephropathy more often had other long-term diabetes complications. However, only 14 of 31 (45%) patients with diabetic nephropathy had concomitant retinopathy (9 of 24 [38%] patients with type 1 diabetes and 5 of 7 [71%] patients with type 2 diabetes, P = 0.198). Autonomic neuropathy was more frequent in patients with than without micro- or macroalbuminuria (P = 0.004).

Glycemic control

Patients with diabetic nephropathy had worse glycemic control during the follow-up period than those without (mean weighted HbA_{1c} 8.1 ± 1.6 vs. 7.2 ± 1.4%, P = 0.001). This was found in both patients with type 1 (HbA_{1c} 8.0 ± 1.9 vs. 7.3 ± 1.4%, P = 0.015) and type 2 diabetes (HbA_{1c} 8.1 ± 1.3 vs. 6.9 ± 1.4%, P = 0.034). Moreover, the occurrence of renal involvement was most frequent among patients with the highest HbA_{1c} values (Fig. 2). In fact, half of the patients with diabetic nephropathy were found among patients in the highest quartile of HbA_{1c} values (i.e., range 8.2–11.2%). Nevertheless, some (n = 5) patients with diabetic nephropathy had HbA_{1c} in the lowest quartile (3.7–6.3%). The range of mean HbA_{1c} values was 5.9–11% among all patients with diabetic nephropathy. Essentially all patients with type 1 diabetes were treated with an intensive insulin regiment and ~95% had four or more daily injections, including CSII, whereas only 2% had less than three injections daily. Among all patients with type 2 dia-

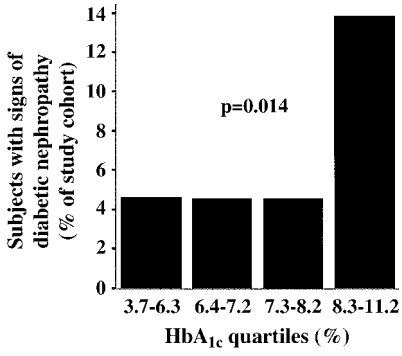

Figure 2—*Prevalence of signs of diabetic nephropathy (DN), i.e., micro- or macroalbuminuria, during follow-up in study cohort divided into quartiles of mean HbA_{1c} levels.*

Table 2—*Cox proportional hazard of risk factors for developing signs of diabetic nephropathy in the DISS 1987–1988 cohort (n = 397)*

Variable	Hazard rate	95% CI	*P*
Sex (male vs. female)	1.78	0.75–4.21	0.19
Type of diabetes* (type 2 vs. type 1)	2.76	0.98–7.74	0.054
Tobacco use (yes vs. no)	0.62	0.28–1.37	0.24
BMI (kg/m^2)	1.01	0.92–1.12	0.79
Mean HbA_{1c} (%)	1.37	1.07–1.75	0.01
Mean arterial blood pressure (mmHg)	1.07	1.02–1.11	0.002

*Type of diabetes after reclassification, see RESEARCH DESIGN AND METHODS.

betes, 24 of 43 (56%) had insulin treatment either alone ($n = 21$) or in combination with oral antidiabetic drugs ($n = 3$). All patients had access to self-monitoring of blood glucose.

Blood pressure and BMI

The mean blood pressure at follow-up was higher among those with than without micro- or macroalbuminuria ($P < 0.001$), in both patients with type 1 and type 2 diabetes ($P = 0.014$ and $P = 0.001$, respectively). In addition, the use of antihypertensive treatment was more prevalent among patients with signs of diabetic nephropathy ($P < 0.001$). Also of note, only 8 of 31 (26%) of all patients with signs of diabetic nephropathy had antihypertensive medication at the time of follow-up (5 of 24 [21%] with type 1 diabetes and 3 of 7 [43%] with type 2 diabetes). BMI was higher in patients with renal involvement ($P = 0.011$); however, when considering patients with type 1 and type 2 diabetes separately, no difference in BMI between those with or without nephropathy ($P = 0.14$ and $P = 0.40$, respectively) was seen. Hence, the association with BMI was due to the increased prevalence of diabetic nephropathy in patients with type 2 diabetes.

Multivariate analysis

A Cox regression analysis model adjusting for sex and tobacco use showed that a high HbA_{1c} level ($P = 0.020$) and high blood pressure ($P = 0.003$) increased the risk for developing nephropathy. A 1% rise in HbA_{1c} was associated with ~30% increased risk of developing renal involvement. There was also a tendency that type 2 diabetes, independent of glycemic control and blood pressure, increased the risk of developing diabetic nephropathy compared with type 1 diabetes, but this difference was uncertain due to a small number of patients ($P = 0.054$) (Table 2). In Fig. 3, a Kaplan-Meier plot shows the cumulative incidence of diabetic nephropathy in type 1 versus type 2 diabetes during a follow-up time of 10 years after diabetes diagnosis.

CONCLUSIONS

— The DISS is a nationwide population-based prospective study of diabetes diagnosed in young adults aged 15–34 years. In this follow-up study, we investigated the early occurrence of diabetic nephropathy in the cohort diagnosed with diabetes from 1987 to 1988. Among the participating patients, 6.6% had exhibited signs of diabetic nephropathy during the follow-up period (median 9 years) following the diagnosis of diabetes. Since patients with type 2 diabetes more often had diabetic nephropathy than those with type 1 diabetes, we may have slightly underestimated the prevalence of diabetic nephropathy in our study, as the nonparticipants were more often reported as having type 2 diabetes. In keeping with this, the nonparticipants for whom medical records were retrieved tended to have a higher occurrence of diabetic nephropathy (9.5%). However, the overall proportion of patients with type 2 diabetes in this age-group is small (~10%), so the indicated overall occurrence of renal involvement should be reasonably representative for the entire age cohort of patients with diabetes. There are few studies of nephropathy in young adults, but the total occurrence of renal involvement in our study is similar to the prevalence of microalbuminuria found after ~15 years duration (7.8%) in the Linkoping study in childhood diabetes with onset during 1976–1980 (5).

Since the median time to follow-up was 9 years, we have identified a subgroup of patients with early onset of renal involvement. The median time to micro- or macroalbuminuria was 8 years. The time course for occurrence of signs of nephropathy in our study appeared to be most rapid for patients with type 2 diabetes, at least during the first 6 years. In addition, the signs of nephropathy tended to be more severe (overt nephropathy) among the patients with type 2 diabetes. This could partly be due to a long period of nondetected hyperglycemia before diagnosis of diabetes, but other components of the metabolic syndrome, such as hypertension and dyslipidema, may have contributed (31). In addition, the proposed link between diabetic nephropathy and insulin resistance and/or the metabolic syndrome (32,33) may be supported by our findings, and shared genetic as well as environmental factors may contribute to this association. However, it should also be noted that insulin resistance may be aggravated by the development and progression of diabetic nephropathy (34,35). Young patients with type 2 diabetes thus seem to have a high risk of early occurrence of diabetic nephropathy, which was also found for

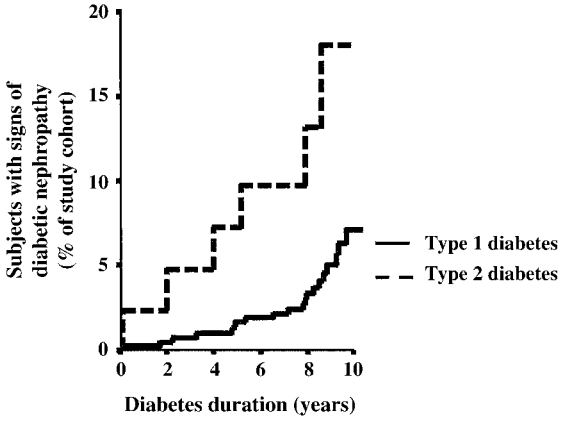

Figure 3—*Signs of diabetic nephropathy (DN) during 10 years of follow-up in type 1 and type 2 diabetes, respectively. Graphs show cumulative incidence obtained by Kaplan-Meier hazard analysis.*

severe retinopathy in the same DISS cohort (20). This highlights the importance of a correct diabetes classification in this age-group, and since clinical diagnosis is difficult (18), measurement of islet antibodies may be recommended.

Although the patients in our study were generally treated with modern diabetes management in the era of the Diabetes Control and Complications Trial (4) and Stockholm studies (14), a few patients developed signs of diabetic nephropathy within 10 years of diabetes diagnosis. As in previous studies, our work indicates that insufficient glycemic control is an important risk factor for the development of micro- or macroalbuminuria, and 50% of these patients were found in the highest quartile of HbA_{1c} values (range 8.2–11.2%). Average HbA_{1c} among patients with type 1 diabetes and signs of diabetic nephropathy ranged from 6.0 to 11.2% in our study. Hence, there are patients with type 1 diabetes who rapidly develop micro- or macroalbuminuria despite reasonable glycemic control, indicating the importance of other risk factors.

Our study confirms that high blood pressure is an important risk marker associated with diabetic nephropathy (9,11,36). Since we only have information on blood pressure at follow-up, we can only speculate that hypertension may have contributed to the development of nephropathy as previously reported (37). When examining the medical records, several of the patients developing early-onset diabetic nephropathy appeared to be noncompliant to treatment recommendations, self-monitoring, and clinical follow-up. Accordingly, in the seven patients with macroalbuminuria, HbA_{1c} and blood pressure tended to be higher than in subjects with microalbuminuria (not significant and $P = 0.04$, respectively); at least four of them had a history of alcohol abuse or psychiatric disorders (data not shown). This is compatible with a previous observation in the DISS cohorts that alcohol abuse and psychiatric disorders are associated with an increased mortality during the first 10 years of diabetes (38). Surprisingly, we did not find any significant association between tobacco use and the occurrence of diabetic nephropathy. Smoking is an established risk factor for the development of albuminuria (39), and it is possible that smoking was underreported both by the responding physicians and in the medical records.

Interestingly, only 14 of 31 (45%) of all patients with diabetic nephropathy had concomitant retinopathy. Among patients with type 1 diabetes and micro- or macroalbuminuria, even fewer (9 of 24 [38%]) had retinopathy. At a first glance this seems to be a surprising finding, but it is indeed in accordance with previous studies (40,41). Moreover, with time, retinopathy will appear in most patients and, particularly, in those with diabetic nephropathy. Most likely, certain genetic polymorphisms have selective impact on the development of nephropathy as compared with retinopathy (42). In patients with type 2 diabetes and signs of diabetic nephropathy, 5 of 7 (71%) had concomitant retinopathy. These findings are important, as absence of retinopathy does not exclude diabetic nephropathy.

In this study, a surprisingly low proportion (8 of 31 [26%]) of the patients with signs of diabetic nephropathy had antihypertensive treatment at follow-up. The reason for this could be that this study was mainly performed before it became generally established that tight blood pressure control and treatment with ACE inhibitors or angiotensin II receptor blockers in patients with microalbuminuria are beneficial (11,13,43).

In conclusion, despite modern diabetes treatment and self-monitoring of blood glucose, there are patients who develop signs of nephropathy during the first 10 years of diabetes. Indeed, this may occur despite reasonably good metabolic control. The main risk markers for development of early-onset diabetic nephropathy, however, were poor glycemic control and high blood pressure. Type 2 diabetes, in itself, was also a risk marker. Hence, a correct classification of diabetes is important. Screening for microalbuminuria should for practical purposes begin as soon as possible after diabetes diagnosis.

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