

Original Article

Good glycemic control remains crucial in prevention of late diabetic complications – the Linköping Diabetes Complications Study

Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J. Good glycemic control remains crucial in prevention of late diabetic complications – the Linköping Diabetes Complications Study. *Pediatric Diabetes* 2009; 10: 168–176.

Background: Several intervention studies have convincingly demonstrated the importance of good glycemic control to avoid long-term diabetic complications, but the importance of other risk factors remains controversial. We previously reported a markedly reduced incidence of severe retinopathy and nephropathy during the past decades in an unselected population of type 1 diabetes mellitus diagnosed in childhood. The aim of the present study was to analyze possible risk factors, which could explain the improved prognosis.

Methods: In this longitudinal population-based cohort study, we followed all 269 patients in whom type 1 diabetes mellitus was diagnosed in childhood 1961–1985 in a well-defined geographical area in Sweden. The patients were followed until the end of 1990s. Multivariable regression models were used to analyze the importance of hemoglobin A_{1c} (HbA_{1c}), diabetes duration, blood pressure, cardiovascular risk factors and persisting C-peptide secretion for the development of diabetic retinopathy and nephropathy.

Results: Beside longer duration and higher HbA_{1c}, blood pressure and lipid values were higher and cardiovascular disease and smoking were more common in patients with severe complications. However, multivariable analysis abolished these associations. Diabetes duration and long-term HbA_{1c} were the only significant independent risk factors for both retinopathy and nephropathy. The risk of overt nephropathy increased substantially when HbA_{1c} was above 9.6% [Diabetes Control and Complications Trial (DCCT) corrected value], while the risk of severe retinopathy increased already when HbA_{1c} exceeded 8.6%.

Conclusion: In this unselected population, glycemic control was the only significant risk factor for the development of long-term complications.

**Maria Nordwall^a,
Hans J Arnqvist^b,
Mats Bojestig^b and
Johnny Ludvigsson^a**

^aDivision of Pediatrics and Diabetes Research Centre, Department of Clinical and Experimental Medicine, Faculty of Health Science, Linköping University, Linköping, Sweden; and ^bDivision of Cell biology and Diabetes Research Centre, Department of Clinical and Experimental Medicine, Faculty of Health Science, Linköping University, Linköping, Sweden

Key words: blood pressure – C-peptide – diabetic nephropathy – diabetic retinopathy – glycosylated – hemoglobin A

Corresponding author:
Maria Nordwall
Division of Pediatrics
Department of Clinical and Experimental Medicine
Faculty of Health Science
Linköping University
SE-581 83 Linköping
Sweden.
Tel: + 46 (11) 22 20 00;
fax: + 46 (11) 22 20 00;
e-mail: maria.nordvall@lio.se

Submitted 15 February 2008. Accepted for publication 5 September 2008

The Diabetes Control and Complications Trial (DCCT) and other intervention studies have convincingly demonstrated the utmost importance of good glycemic control to avoid long-term complications (1). In unselected populations, it is difficult to achieve as good glycemic control as in intervention trials (2, 3). Despite intensive treatment from diagnosis, hemoglobin A_{1c} (HbA_{1c}) values are higher than those in the DCCT study, where average HbA_{1c} was 7.2% in the intensive treatment group (1) and far from the newly

recommended level of HbA_{1c} <6.0% in guidelines from the American Diabetes Association. Studies concerning the importance of smoking, blood pressure, and other cardiovascular risk factors associated with the metabolic syndrome have shown diverging results.

In previous analysis, we found a declining incidence of severe retinopathy and a persisting decrease of overt nephropathy during the past decades in an unselected population with type 1 diabetes mellitus diagnosed in childhood (4, 5). The aim of the present study was to

analyze possible risk factors, which could explain the improved prognosis in this population.

Methods

The study design is an observational study, which started in 1961. Since 1976, data were collected prospectively for severe retinopathy, overt diabetic nephropathy, blood pressure, C-peptide, and metabolic control. The study was complemented with cross-sectional data in the end of the 1990s concerning cardiovascular risk factors and any grades of diabetic retinopathy and nephropathy.

Patients

We studied all 269 patients with type 1 diabetes mellitus diagnosed before the age of 15 yr during 1961–1985 in the catchment area of the Pediatric Clinic, Linköping, Sweden. After the age of 19 yr, the patients were transferred to the Department of Internal Medicine. The population was followed until the end of the 1990s, mostly between the years 1998–1999. The majority of the patients, 214 (80%), remained in the catchment area, and information was collected from their medical records. For the patients, who had moved, information was collected through their physicians. Three patients went abroad within 5 yr after diabetes diagnosis. In total, 26 patients have died, 12 of them before developing retinopathy and 7 before developing nephropathy. Of the total population, 244 (91%) were monitored for retinopathy and 255 (95%) for nephropathy until at least 1997. The rest of the patients were followed until their most recent clinical visit.

For analysis of clinical characteristics, the patients were divided into five cohorts according to the year of diabetes diagnosis. The groups were similar in number of patients, sex distribution, mean age at onset of diabetes, and proportion diagnosed before puberty (Table 1).

The Research Ethics Committee at the Faculty of Health Sciences, Linköping University, approved the study.

Definitions

Retinopathy. The patients were screened regularly for retinopathy, usually every second year, after the beginning of puberty. Until the 1970s, the screening procedure was ophthalmoscopy and later on color fundus photography. All photographs were examined by ophthalmologists and in a standard protocol categorized into four classes on the basis of the worst eye, namely, into normal, simplex retinopathy, preproliferative retinopathy, or proliferative retinopathy. The patients who had left the catchment area were examined at their local hospital with the same grading system.

Table 1. Clinical characteristics of patients with type 1 diabetes diagnosed in childhood during five different time periods

Characteristics	1961–1965 (n = 56)	1966–1970 (n = 50)	1971–1975 (n = 55)	1976–1980 (n = 51)	1981–1985 (n = 57)	All periods (n = 269)
Age at onset, mean (SD), yr	8.5 (3.5)	8.0 (3.9)	8.8 (4.0)	8.7 (3.8)	8.9 (3.8)	8.6 (3.8)
Diabetes duration at last follow-up of retinopathy, mean (SD), yr	35.4 (1.8), n = 55	30.2 (2.6), n = 48	25.3 (2.5), n = 55	20.1 (2.2), n = 51	14.9 (2.1), n = 55	25.2 (7.6), n = 264
Diabetes duration at last follow-up of nephropathy, mean (SD), yr	35.5 (1.6), n = 56	30.8 (2.6), n = 49	25.5 (2.5), n = 55	20.6 (2.1), n = 51	15.0 (1.7), n = 55	25.5 (7.6), n = 266
Patients with background retinopathy, n (%)	19 (34.5)	24 (50.0)	34 (61.8)	28 (54.9)	26 (47.3)	131 (49.6)
Patients with severe retinopathy, n (%)	32 (58.2)	19 (39.6)	13 (23.6)	3 (5.9)	2 (3.6)	69 (26.1)
Patients with microalbuminuria, n (%)	7 (12.5)	3 (6.1)	4 (7.3)	3 (5.9)	3 (5.9)	20 (7.5)
Patients with overt nephropathy, n (%)	22 (39.3)	5 (10.2)	7 (12.7)	1 (2.0)	1 (1.8)	36 (13.5)

Onset of severe retinopathy was defined as the date of the first laser treatment of proliferative retinopathy or maculopathy. At the last follow-up, in the end of the 1990s, the presence of any retinopathy was defined as background retinopathy (simplex or preproliferative retinopathy), proliferative retinopathy, or previous laser treatment.

Nephropathy. All patients were tested for proteinuria at their regular clinic visits with a semi-quantitative test strip (Albustix®, Bayer Diagnostics, Tarrytown, NY, USA). During the past decades, the patients, at least once every year, had a morning sample of urine analyzed by quantitative method at the local hospital laboratory. For patients moving to other parts of Sweden, analysis was made at the local hospitals with similar methods.

Overt diabetic nephropathy was defined as persistent proteinuria, that is at least the result 1 + on the test strip (which corresponds to an albumin concentration in the urine of >300 mg/L) or with quantitative method albumin excretion rate (AER) > 200 µg/min or albumin concentration >300mg/L. The onset was defined as the first year during which proteinuria became persistent. When the proteinuria had become persistent, in no cases it returned to normal in this population. Microalbuminuria was defined as AER 20–200 µg/min or albumin concentration 30–300 mg/L in the last available urine sample at the last follow-up in the end of the 1990s. This is a wider definition as usually used, but in this clinically followed population, the urine samples were not consistently collected and many patients had not enough samples to use the definition of two-third positive samples during 6 months. The presence of any nephropathy was defined as microalbuminuria or persistent proteinuria.

Glycemic control. Analysis of HbA₁ and HbA_{1c} was introduced in 1980 and 1986, respectively, and was measured regularly at the clinical visits three to four times per year. From the analyzing laboratory, there were calculated intermethod calibrations and conversion factors every time when the methods were changed. After 1996, the method has been calibrated against the Swedish national standard Mono-S and continuously controlled against the External Quality Assurance in Laboratory medicine in Sweden (EQUALIS) reference method. For the patients who moved, it has been possible to obtain their HbA_{1c} values by their physicians and conversions factors to the EQUALIS reference method by the local laboratory. In this study, all values were first converted by formulas to the EQUALIS reference values with normal range 3.6–5.0%. The values were then transformed to the corresponding DCCT values by adding 1.1% (6).

As a measure of long-term glycemic control for each patient, mean HbA_{1c} was calculated and weighted for the time between the measurements. All HbA_{1c} values until the year of onset of severe retinopathy and overt nephropathy, respectively, were included in the calculations. HbA_{1c} values were not available for 17 (47%) of the 36 patients with overt nephropathy and 17 (25%) of the 69 patients with severe retinopathy as the complications occurred before the introduction of the HbA₁ measurements.

Cardiovascular risk factors. Blood pressure was measured regularly at the clinical visits. Long-term blood pressure was calculated as a mean of all measurements until the year of onset of severe retinopathy and overt nephropathy, respectively, and weighted for different time intervals between the measurements. Blood pressure before 18 yr of age was excluded because of difficulties to compare values in childhood with adult values. Of the whole population, 45 (17%) used antihypertensive therapy at follow-up. Of these, 25 (55%) were prescribed before diagnosis of overt nephropathy and 18 (40%) before diagnosis of severe retinopathy. Body mass index (BMI) was calculated as weight (kg)/height² (m) and recorded at the last follow-up. History of cardiovascular disease (CVD) (stroke, myocardial infarction, cardiac failure, or symptoms of arteriosclerosis) was collected from the patients' medical record or their physician. Lipids were not analyzed regularly until the late 1990s. Information was available for 199 (74%) of the total population, for 41 (58%) of 69 patients with severe retinopathy and for 21 (58%) of 36 patients with overt nephropathy. The lower rate in these groups is explained by the higher mortality. The reference value was <5 mmol/L for cholesterol and <1.7 mmol/L for triglycerides.

A questionnaire was answered by 183 (68%) patients in the end of the 1990s, where they reported smoking habits. History of smoking was defined as former or current smoking more than one cigarette per day. Heredity for type 2 diabetes mellitus, hypertension, and CVD in first- and second-degree relatives was also reported.

C-peptide. From 1976 onwards, fasting C-peptide was analyzed yearly in children with newly diagnosed diabetes until they left the pediatric clinic or C-peptide was not detected for three consecutive years. The normal fasting reference value in non-diabetic children is 0.18–0.63 nmol/L. For this study, the presence of C-peptide >0.1 nmol/L after 5 yr of diabetes duration was stated.

Statistical analysis

Univariate comparisons of groups were performed with Student's *t*-test or one-way ANOVA for differences of means with Bonferroni-adjusted pairwise comparisons.

Chi-square or Fischer's exact test was used for proportions. Cox proportional hazard analysis was used to analyze the influence of possible risk factors for the occurrence of severe retinopathy and overt nephropathy. Logistic regression models adjusting for HbA_{1c} and diabetes duration were used to analyze the relation between the risk factors and the presence of any nephropathy and any retinopathy at the follow-up in the end of 1990s. A multivariable logistic regression model with all relevant risk factors were tested but had to be restricted to those 143 (52%) individuals who had complete data in all included variables. Odds ratios (OR) with 95% confidence interval (CI) were estimated. For analyzing effects of good and poor glycemic control, the patients were divided into four groups according to their long-term HbA_{1c} values. The cumulative proportion of severe laser-treated retinopathy and overt nephropathy was then calculated for 1-yr intervals using a life table method. The differences between all groups and pairwise comparisons were tested using the Wilcoxon (Gehan) log-rank statistic test. $p < 0.05$ was considered statistically significant. The calculations were performed in SPSS 11.5.

Results

The occurrences of risk factors for long-term complications at the follow-up in the end of 1990s were compared between the cohorts (Table 2). There was

a significant difference only regarding systolic blood pressure, which was highest in the oldest cohort, and smoking and CVD, which were more prevalent in the oldest cohort too. The long-term glycemic control, diastolic blood pressure, BMI, and lipids were similar in all groups as well as heredity factors and persistence of C-peptide secretion.

The occurrence of risk factors among the patients with and without diabetic complications at the follow-up in the end of 1990s was compared in Tables 3 and 4. Diabetes duration was longer and HbA_{1c} was significantly higher as well as blood pressure and cholesterol values in patients with any grade of eye complications. The prevalence of CVD and smoking was higher among patients with severe retinopathy. In contrast, BMI, triglycerides, persistence of C-peptide secretion the first 5 yr after diagnosis, and heredity for CVD or type 2 diabetes mellitus did not differ significantly between the groups. The same pattern was seen among patients with overt nephropathy. For patients with microalbuminuria, there was a significant difference compared with patients with no complications only for CVD, smoking, and lipids and not for duration, glycemic control, or blood pressure.

The relation between possible risk factors and prevalence of any retinopathy and any nephropathy at follow-up was analyzed with the use of logistic regressions models, adjusting for the possible confounding effects of glycemic control and diabetes

Table 2. Possible risk factors for long-term complications in patients with type 1 diabetes during five different time periods

Risk factor	Period of onset					p-Value
	1961–1965	1966–1970	1971–1975	1976–1980	1981–1985	
Long-term hemoglobin A1c, % (SD), n = 253	8.6 (0.9)	8.5 (0.8)	8.5 (0.9)	8.4 (1.1)	8.2 (0.9)	0.19
Systolic blood pressure, mean (SD), mmHg, n = 255	127 (8)	125 (11)	122 (8)	122 (8)	122 (8)	0.005
Diastolic blood pressure, mean (SD), mmHg, n = 255	78 (6)	76 (6)	76 (5)	76 (4)	77 (6)	0.20
History of smoking, %, n = 183	71.4	53.6	46.5	31.6	30.8	0.002
Body mass index, mean (SD), kg/m ² , n = 241	25.7 (3.5)	25.5 (3.4)	26.0 (4.2)	25.6 (3.3)	24.9 (3.6)	0.63
Total cholesterol, mean (SD), mmol/L*, n = 199	5.3 (1.0)	4.9 (0.8)	5.0 (1.1)	4.8 (0.8)	4.6 (1.0)	0.05
Triglycerides, mean (SD), mmol/L†, n = 199	1.5 (0.7)	1.2 (0.6)	1.3 (1.2)	1.2 (0.9)	1.3 (0.9)	0.78
History of CVD, %, n = 256	25.0	13.0	7.5	0	0	<0.001
C-peptide >0.1 nmol/L during first 5 yr, %, n = 103				4.1	15.1	0.10
Heredity hypertension, %, n = 183	42.9	39.3	37.2	34.2	43.6	0.91
Heredity CVD, %, n = 183	57.1	53.6	44.2	54.1	51.3	0.83
Heredity type 2 diabetes, %, n = 183	31.4	42.9	32.6	31.6	33.3	0.88

CVD, cardiovascular disease.

Number of patients with available data differs between factors and is indicated by n.

Data for C-peptide are available only for patients with diabetes onset later than 1975.

*To convert cholesterol from mmol/L to mg/dL, divide by 0.0259.

†To convert triglycerides from mmol/L to mg/dL, divide by 0.0113.

Table 3. Possible risk factors in patients with type 1 diabetes diagnosed in childhood with and without retinopathy

Risk factor	No retinopathy, n = 64	Background retinopathy, n = 131	Severe laser-treated retinopathy, n = 69	p-Value
Diabetes duration, mean (SD), yr	19.7 (6.3)	24.3 (6.9)	31.7 (6.3)	<0.001*
Long-term hemoglobin A1c, % (SD)	7.8 (0.8), n = 62	8.5 (0.8), n = 130	9.0 (1.0), n = 52	<0.001*
Systolic blood pressure, mean (SD), mmHg	120.4 (8.7), n = 60	123.8 (7.8), n = 130	128.5 (13.4), n = 54	<0.001†
Diastolic blood pressure, mean (SD), mmHg	74.6 (5.9), n = 60	76.7 (4.4), n = 130	80.8 (7.3), n = 54	<0.001†
History of smoking, %	36.4, n = 44	40.8, n = 98	68.3, n = 41	0.004
Body mass index, mean (SD), kg/m ²	24.6 (3.7), n = 59	25.9 (3.5), n = 128	25.6 (3.5), n = 54	0.06
Total cholesterol, mean (SD), mmol/L‡	4.5 (0.8), n = 44	5.0 (1.1), n = 114	5.1 (0.9), n = 41	0.004†
Triglycerides, mean (SD), mmol/L§	1.1 (0.5), n = 44	1.4 (1.1), n = 114	1.4 (0.6), n = 41	0.11
History of CVD, %	3.2, n = 62	3.9, n = 129	24.6, n = 65	<0.001
C-peptide >0.1 nmol/L during first 5 yr, %	8.9, n = 45	9.8, n = 51	20, n = 5	1.0
Heredity hypertension, %	34.1, n = 44	41.8, n = 98	39.0, n = 41	0.68
Heredity CVD, %	52.3, n = 44	49.5, n = 97	56.1, n = 41	0.77
Heredity type 2 diabetes, %	38.6, n = 44	30.6, n = 98	36.6, n = 41	0.59

CVD, cardiovascular disease.

Number of patients with available data differs between risk factors and is indicated by n.

Data for C-peptide are available only for patients with diabetes onset later than 1975.

*Significant difference ($p < 0.05$) between all three groups in pairwise comparison.

†Significant difference ($p < 0.05$) between severe or background retinopathy and no retinopathy.

‡To convert cholesterol from mmol/L to mg/dL, divide by 0.0259.

§To convert triglycerides from mmol/L to mg/dL, divide by 0.0113.

duration (Table 5). Of the univariate associations, only systolic and diastolic blood pressure were still significant risk factors concerning retinopathy and diastolic blood pressure and lipids concerning nephropathy. Even these relations were abolished when all possible risk factors were tested in a multivariable model. Only diabetes duration OR (95% CI) 1.2 (1.1–1.3) ($p < 0.001$) and HbA_{1c} OR (95% CI) 4.1 (1.8–9.2) ($p = 0.001$) showed a significant correlation to any retinopathy. All other factors were insignificant. The same pattern was seen concerning any nephropathy where diabetes duration OR (95% CI) 1.1 (1.0–1.2) ($p = 0.016$) and HbA_{1c} OR (95% CI) 2.6 (1.3–5.1) ($p = 0.007$) showed a significant association.

The influence of possible risk factors on the occurrence of overt nephropathy and severe retinopathy was analyzed with Cox regression models. When the significant variables in the univariate analysis were entered in the model, the only significant variable for occurrence of retinopathy was HbA_{1c}, hazard rate (95% CI) 2.1 (1.2–3.4) ($p = 0.005$) and for development of nephropathy HbA_{1c}, hazard rate (95% CI) 5.3 (2.3–12.4) ($p < 0.001$). Other models with other combinations of variables yielded the same result with HbA_{1c} as the only significant variable (data not shown).

The cumulative proportion of severe retinopathy and overt nephropathy for patients with different long-term HbA_{1c} is illustrated in Fig. 1A, B. The risk of

retinopathy is increasing significantly if long-term HbA_{1c} is higher than 8.6%. In contrast, the risk of overt nephropathy is increasing significantly first when HbA_{1c} values increase above 9.6%.

Discussion

After adjustment for other possible confounding factors, glycemic control and diabetes duration remained the only significant risk factors for diabetic retinopathy and nephropathy. The risk for severe complications was very low in patients with long-term HbA_{1c} below 8.6% and 9.6% for retinopathy and nephropathy, respectively, and no patient with HbA_{1c} below 7.6% had overt nephropathy despite long duration.

Only intervention studies can give a definitive answer whether associations between risk factors are causal. However, long-term intervention studies tend to include especially motivated patients with conditions that differ from real life. Our population is an unselected population because every child in Sweden is treated at a pediatric clinic. We managed to follow the patients during a long time with only a few dropouts. However, the long follow-up time means also difficulties because laboratory methods and definition of complications could have changed during time. The HbA₁

Table 4. Possible risk factors in patients with type 1 diabetes diagnosed in childhood with and without nephropathy

Risk factor	No nephropathy, n = 210	Microalbuminuria, n = 20	Overt nephropathy, n = 36	p-Value
Diabetes duration, mean (SD), yr	24.1 (7.3)	28.0 (7.8)	32.2 (5.6)	<0.001*
Long-term hemoglobin A1c, % (SD)	8.3 (0.9), n = 206	8.7 (0.9), n = 19	9.7 (1.1), n = 19	<0.001†
Systolic blood pressure, mean (SD), mmHg	123.3 (8.9), n = 205	123.8 (9.0), n = 19	128.0 (6.3), n = 31	0.02*
Diastolic blood pressure, mean (SD), mmHg	76.1 (5.1), n = 205	77.8 (4.6), n = 19	80.7 (6.5), n = 31	<0.001*
History of smoking, %	40.3, n = 149	68.8, n = 16	72.2, n = 18	0.006
Body mass index, mean (SD), kg/m ²	25.3 (3.5), n = 197	25.6 (3.5), n = 19	27.1 (4.5), n = 25	0.07
Total cholesterol, mean (SD), mmol/L‡	4.8 (0.9), n = 163	5.5 (1.4), n = 15	5.5 (1.0), n = 21	<0.001§
Triglycerides, mean (SD), mmol/L¶	1.2 (0.8), n = 163	2.0 (1.6), n = 15	1.6 (0.5), n = 21	0.001**
History of CVD, %	3.9, n = 206	20.0, n = 20	36.7, n = 30	<0.001
C-peptide >0.1 nmol/L during first 5 yr, %	9.7, n = 93	16.7, n = 6	0.0, n = 2	1.0
Heredity hypertension, %	40.9, n = 149	31.3, n = 16	33.3, n = 18	0.65
Heredity CVD, %	53.4, n = 148	37.5, n = 16	50.0, n = 18	0.48
Heredity type 2 diabetes, %	35.6, n = 149	31.3, n = 16	22.2, n = 18	0.51

CVD, cardiovascular disease.

Number of patients with available data differs between risk factors and is indicated by n.

Data for C-peptide are available only for patients with diabetes onset later than 1975.

*Significant difference ($p < 0.05$) between overt nephropathy and no nephropathy.

†Significant differences ($p < 0.05$) between overt nephropathy and microalbuminuria and no nephropathy, respectively.

‡To convert cholesterol from mmol/L to mg/dL, divide by 0.0259.

§Significant difference ($p < 0.05$) between overt nephropathy/microalbuminuria and no nephropathy.

¶To convert triglycerides from mmol/L to mg/dL, divide by 0.0113.

**Significant difference between microalbuminuria and no nephropathy.

method changed several times, but the laboratory had conversion equations between the different methods, which made comparisons possible. The method of AER also changed, and some of the samples were measured at different centers.

The HbA_{1c} measurement was introduced in 1980, and a relatively large number of the patients could not be included in the analysis because their complications

were diagnosed before 1980. The same is valid to the lipid data because lipids were not routinely analyzed until recent years. Another limitation of the study is that some patients started antihypertensive medication before the development of microvascular disease, and we cannot exclude that this has delayed or prevented nephropathy or retinopathy. We tried to include all possible confounding variables in the analysis because

Table 5. Risk factors for any retinopathy and any nephropathy after adjustment for glycemic control (hemoglobin A1c) and diabetes duration

Risk factor	Any retinopathy		Any nephropathy	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Systolic blood pressure (mmHg)	1.06 (1.01–1.11)	0.02	1.02 (0.97–1.06)	0.48
Diastolic blood pressure (mmHg)	1.10 (1.02–1.18)	0.02	1.09 (1.01–1.18)	0.03
History of smoking	0.61 (0.25–1.50)	0.28	1.82 (0.73–4.53)	0.20
Body mass index (kg/m ²)	1.0 (0.9–1.2)	0.55	1.0 (0.9–1.2)	0.51
Total cholesterol (mmol/L)	1.27 (0.77–2.08)	0.35	1.68 (1.10–2.56)	0.02
Triglycerides (mmol/L)	1.06 (0.60–1.87)	0.84	1.5 (1.00–2.26)	0.05
History of CVD	0.28 (0.04–1.9)	0.19	3.06 (0.91–10.34)	0.07
C-peptide >0.1 nmol/L during first 5 yr of diabetes	3.79 (0.67–21.35)	0.13	1.76 (0.17–18.75)	0.64
Heredity hypertension	1.50 (0.63–3.54)	0.36	0.88 (0.35–2.20)	0.79
Heredity CVD	0.66 (0.28–1.56)	0.34	0.56 (0.23–1.36)	0.20
Heredity type 2 diabetes	0.61 (0.25–1.45)	0.26	0.73 (0.28–1.90)	0.51

95% CI, 95% confidence interval; CVD, cardiovascular disease; OR, odds ratio.

OR for dichotomous variables has as reference group those patients without the respective factor.

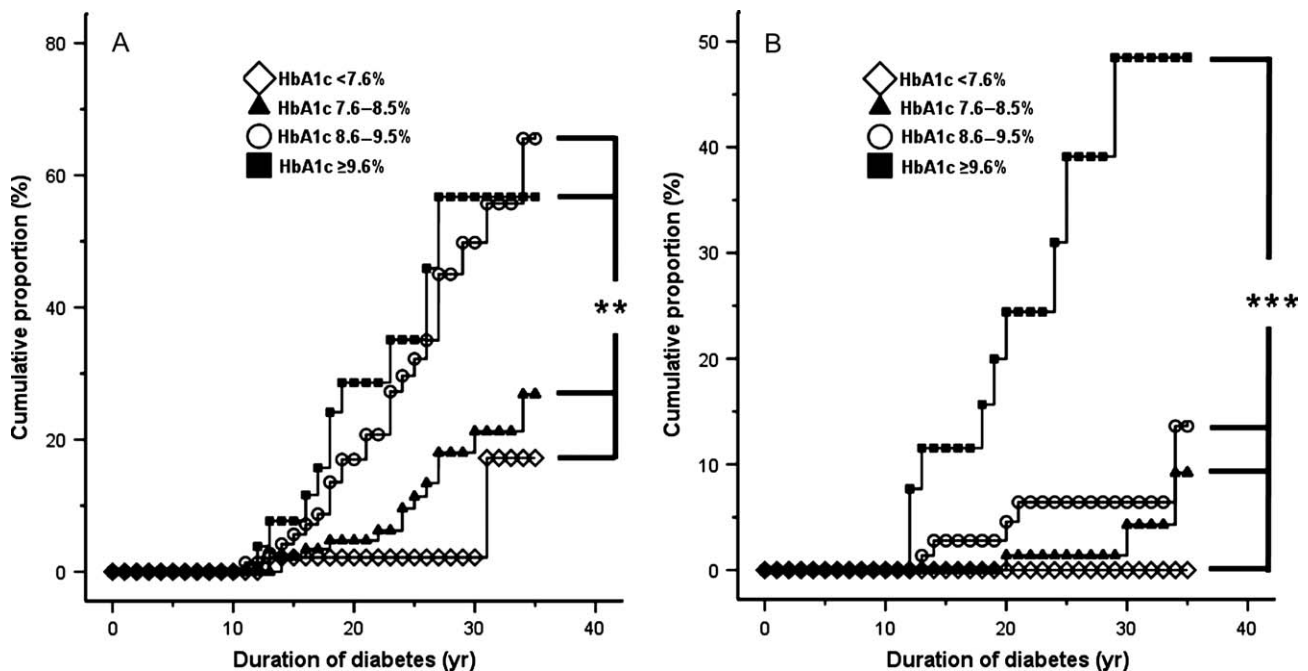


Fig. 1. Cumulative proportion of (A) severe retinopathy and (B) overt nephropathy in a population of type 1 diabetes diagnosed in childhood according to long-term glycemic control. $p < 0.001$ for overall comparison of groups. In pairwise comparison, $p < 0.01$ between groups indicated in the figure with ** and $p < 0.001$ with***.

there is a complex interrelationship between risk factors in this type of observational study. However, introduction of several variables in the analysis can diminish the possibility to really discover significant associations, especially if the population is rather small as in our study. In the multivariable models, the analysis had to be restricted to patients with available data on all variables, which diminished the statistical power still more. We cannot exclude that lack of association could partly be explained by too low statistical power.

The higher systolic blood pressure in the oldest cohorts can partly be explained by the pressure rising with age. Both systolic and diastolic pressures were higher in patients with any retinopathy and overt nephropathy. The association persisted for diastolic pressure even after adjusting for duration and HbA_{1c} but for systolic pressure only concerning retinopathy. Even if many studies have demonstrated the value of antihypertensive treatment to retard the progress of kidney damage (7), the role of blood pressure as a pathogenetic factor for initial development of complications remains uncertain (8). Some studies report an association between nephropathy (9), retinopathy (10), and higher blood pressure, while other studies have failed to detect such correlations (1, 11). We analyzed long-term blood pressure, which could underestimate the effect. However, if only the past year's blood pressure is taken into consideration, there is a risk of overestimating the causal relationship if higher blood pressure is a consequence rather than

a cause of early nephropathy. Renal structural abnormalities are present long before they are possible to detect with usual laboratory tests (12).

BMI was the same in all cohorts and did not differ significantly between patients with and without complications. This is in concordance with some studies (13), while others have found BMI to be a risk factor for both nephropathy and retinopathy (8, 14).

There was no difference of lipid values among cohorts but significantly higher cholesterol values in patients with both retinopathy and nephropathy and also higher triglycerides in the latter group. The association was abolished in multivariable regression models, again emphasizing the importance of glycemic control. Some studies have found correlations between higher lipoproteins values and complications (8, 9), while others have failed to show that concerning retinopathy (13).

CVD was more common in the older cohorts, which can be explained by the older age in these groups. Microvascular complications were however more common in these cohorts, and there was a strong association between CVD and severe retinopathy, microalbuminuria, and above all overt nephropathy, demonstrated in many other studies (15–17). When adjusting for diabetes duration and HbA_{1c}, the association was abolished, again speaking in favor of glycemic control as the main factor. A common pathogenetic factor, for example glycemic control, explaining both CVD and microvascular complications

has been suggested (17). The higher prevalence of classic cardiovascular risk factors in patients with nephropathy, demonstrated also in our study, could be another explanation (15, 16).

Smoking was more prevalent in the oldest cohort. More than 70% were current or former smokers. The prevalence declined gradually among the younger cohorts. This is probably a cohort phenomenon as the smoking habits have decreased substantially in Sweden the past decades. We found higher prevalence of smokers in patients with severe retinopathy and any nephropathy, but the association disappeared when adjusting for duration and glycemic control. Thus, smoking habits do not seem to explain the higher incidence of complications in the oldest cohorts. Other studies have given conflicting evidence concerning the connection with nephropathy and especially retinopathy (18, 19). Glycemic control could be a confounding factor. Psychosocial factors may affect both smoking habits and the ability to achieve good glycemic control (19).

The proportion of patients with persisting C-peptide the first years after diagnosis did not differ between cohorts or patients with or without complications. The DCCT study showed a slower progress of complications in patients with C-peptide secretion (20). However, the follow-up was shorter than that in our study. It is reasonable that the effect of persistent C-peptide secretion during the first years diminishes in importance in a long time perspective as the C-peptide secretion gradually decreases in the years after diabetes onset (20). There are few other studies in this field, and no one could demonstrate a long-term effect of C-peptide when adjusting for glycemic control (21).

Heredity for CVD, type 2 diabetes mellitus, and hypertension did not differ between cohorts or patients with and without complications. Several studies have shown clustering of diabetic nephropathy (22) and retinopathy in families (23), but there are divergent ideas concerning the importance of heredity for CVD (24), type 2 diabetes mellitus (25, 26), hypertension (27), and the risk of nephropathy. Our result does not support the hypothesis that inheritance of metabolic syndrome explains the genetic susceptibility to long-term complications (28).

In our previous study (2), we found a declining incidence of both severe retinopathy and overt nephropathy in this population. This study shows that bad glycemic control is the most important risk factor for development of microvascular complications. We did not find a difference between the cohorts concerning long time HbA_{1c}. However, before 1980, there were no measurements of HbA_{1c} and we therefore do not know the degree of glycemic control during the 1960s and 1970s for the oldest cohorts. During the 1960s, the insulin regimen was less intensive with just one dose of insulin per day, which increased to two to three during the 1970s but still with no self monitoring of blood

glucose. Thus, it is reasonable to assume that glycemic control was worse especially during the 1960s and that better glycemic control is the main factor for the improved prognosis thereafter. This may be especially important for the long-term prognosis as the glycemic control during the first years of diabetes seems to have an important role for future complications (29).

In conclusion, good glycemic control is the most crucial factor for prevention of long-term microvascular complications. We could not confirm the importance of long-term blood pressure, lipid profiles, CVD, BMI, and smoking in this unselected population of type 1 diabetes mellitus. All efforts must be focused on achievement of as good glycemic control as possible even though some recent recommendations may be unnecessarily strict for prevention of severe microvascular complications.

Acknowledgements

This study was supported by the Juvenile Diabetes Research Foundation International (JDRF)-Wallenberg (K2002-99JD-12813-05E), the Swedish Research Council (VR) K2002-72X-11242-08A, and the Swedish Child Diabetes Foundation (Barndiabetesfonden).

References

1. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329: 977–986.
2. NORDWALL M, HYLLIENMARK L, LUDVIGSSON J. Early diabetic complications in a population of young patients with type 1 diabetes mellitus despite intensive treatment. *J Pediatr Endocrinol Metab* 2006; 19: 45–54.
3. OLSEN BS, JOHANNESSEN J, SJOLIE AK et al. Metabolic control and prevalence of microvascular complications in young Danish patients with type 1 diabetes mellitus. Danish Study Group of Diabetes in Childhood. *Diabet Med* 1999; 16: 79–85.
4. BOJESTIG M, ARNQVIST HJ, HERMANSSON G, KARLBERG BE, LUDVIGSSON J. Declining incidence of nephropathy in insulin-dependent diabetes mellitus. *N Engl J Med* 1994; 330: 15–18.
5. NORDWALL M, BOJESTIG M, ARNQVIST HJ, LUDVIGSSON J. Declining incidence of severe retinopathy and persisting decrease of nephropathy in an unselected population of type 1 diabetes-the Linköping Diabetes Complications Study. *Diabetologia* 2004; 47: 1266–1272.
6. KULLBERG CE, BERGSTROM A, DINESEN B et al. Comparisons of studies on diabetic complications hampered by differences in GHb measurements. *Diabetes Care* 1996; 19: 726–729.
7. LEWIS EJ, HUNSICKER LG, BAIN RP, ROHDE RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993; 329: 1456–1462.
8. CHATURVEDI N, BANDINELLI S, MANGILI R, PENNO G, ROTTIERS RE, FULLER JH. Microalbuminuria in type 1 diabetes: rates, risk factors and glycemic threshold. *Kidney Int* 2001; 60: 219–227.

9. EBELING P, KOIVISTO VA. Occurrence and interrelationships of complications in insulin-dependent diabetes in Finland. *Acta Diabetol* 1997; 34: 33–38.
10. SJOLIE AK, STEPHENSON J, ALDINGTON S et al. Retinopathy and vision loss in insulin-dependent diabetes in Europe. The EURODIAB IDDM Complications Study. *Ophthalmology* 1997; 104: 252–260.
11. KLEIN R, ZINMAN B, GARDINER R et al. The relationship of diabetic retinopathy to preclinical diabetic glomerulopathy lesions in type 1 diabetic patients: the Renin-Angiotensin System Study. *Diabetes* 2005; 54: 527–533.
12. DRUMMOND K, MAUER M. The early natural history of nephropathy in type 1 diabetes: II. Early renal structural changes in type 1 diabetes. *Diabetes* 2002; 51: 1580–1587.
13. DE BLOCK CE, DE LEEUW IH, VAN GAAL LF. Impact of overweight on chronic microvascular complications in type 1 diabetic patients. *Diabetes Care* 2005; 28: 1649–1655.
14. ZHANG L, KRZENTOWSKI G, ALBERT A, LEFEBVRE PJ. Risk of developing retinopathy in diabetes control and complications trial type 1 diabetic patients with good or poor metabolic control. *Diabetes Care* 2001; 24: 1275–1279.
15. KLEIN BE, KLEIN R, MCBRIDE PE et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. *Arch Intern Med* 2004; 164: 1917–1924.
16. TORFFVIT O, LOVESTAM-ADRIAN M, AGARDH E, AGARDH CD. Nephropathy, but not retinopathy, is associated with the development of heart disease in type 1 diabetes: a 12-year observation study of 462 patients. *Diabet Med* 2005; 22: 723–729.
17. VAN HECKE MV, DEKKER JM, STEHOUWER CD et al. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. *Diabetes Care* 2005; 28: 1383–1389.
18. SAWICKI PT, DIDJURGEIT U, MUHLHAUSER I, BENDER R, HEINEMANN L, BERGER M. Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 1994; 17: 126–131.
19. CHATURVEDI N, STEPHENSON JM, FULLER JH. The relationship between smoking and microvascular complications in the EURODIAB IDDM Complications Study. *Diabetes Care* 1995; 18: 785–792.
20. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. *Ann Intern Med* 1998; 128: 517–523.
21. WINOCOUR PH, JEACOCK J, KALSI P, GORDON C, ANDERSON DC. The relevance of persistent C-peptide secretion in type 1 (insulin-dependent) diabetes mellitus to glycaemic control and diabetic complications. *Diabetes Res Clin Pract* 1990; 9: 23–35.
22. SEAQUIST ER, GOETZ FC, RICH S, BARBOSA J. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med* 1989; 320: 1161–1165.
23. Clustering of long-term complications in families with diabetes in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes* 1997; 46: 1829–1839.
24. EARLE K, WALKER J, HILL C, VIBERTI G. Familial clustering of cardiovascular disease in patients with insulin-dependent diabetes and nephropathy. *N Engl J Med* 1992; 326: 673–677.
25. FAGERUDD JA, PETTERSSON-FERNHOLM KJ, GRONHAGEN-RISKA C, GROOP PH. The impact of a family history of type II (non-insulin-dependent) diabetes mellitus on the risk of diabetic nephropathy in patients with type I (insulin-dependent) diabetes mellitus. *Diabetologia* 1999; 42: 519–526.
26. ROGLIC G, COLHOUN HM, STEVENS LK, LEMKES HH, MANES C, FULLER JH. Parental history of hypertension and parental history of diabetes and microvascular complications in insulin-dependent diabetes mellitus: the EURODIAB IDDM Complications Study. *Diabet Med* 1998; 15: 418–426.
27. BARZILAY J, WARRAM JH, BAK M, LAFFEL LM, CANESSA M, KROLEWSKI AS. Predisposition to hypertension: risk factor for nephropathy and hypertension in IDDM. *Kidney Int* 1992; 41: 723–730.
28. ORCHARD TJ, CHANG YF, FERRELL RE, PETRO N, ELLIS DE. Nephropathy in type 1 diabetes: a manifestation of insulin resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh Epidemiology of Diabetes Complication Study. *Kidney Int* 2002; 62: 963–970.
29. SVENSSON M, ERIKSSON JW, DAHLQUIST G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. *Diabetes Care* 2004; 27: 955–962.