

# Discordant Trends in Microvascular Complications in Adolescents With Type 1 Diabetes From 1990 to 2002

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**OBJECTIVE** — Since the Diabetes Control and Complications Trial, diabetes management goals have changed. The aims of the present study were to assess complication rates, including nerve abnormalities, in adolescents from 1990 to 2002 and to investigate associated risk factors.

**RESEARCH DESIGN AND METHODS** — Cross-sectional analysis of complications was assessed in three study periods (1990–1994 [T1], 1995–1998 [T2], and 1999–2002 [T3]) in adolescents matched for age and diabetes duration ( $n = 878$ , median age 14.6 years, median duration 7.5 years). Retinopathy was assessed by seven-field stereoscopic fundal photography, albumin excretion rate (AER) from three consecutive timed overnight urine collections, peripheral nerve function by thermal and vibration thresholds, and autonomic nerve function by cardiovascular reflexes.

**RESULTS** — Retinopathy declined significantly (T1, 49%; T2, 31%; and T3, 24%;  $P < 0.0001$ ), early elevation of AER ( $\geq 7.5 \mu\text{g}/\text{min}$ ) declined (38, 30, and 25%, respectively,  $P = 0.022$ ), and microalbuminuria (AER  $\geq 20 \mu\text{g}/\text{min}$ ) declined (7, 3, and 3%, respectively;  $P = 0.017$ , T1 vs. T2 and T3). Autonomic nerve abnormalities were unchanged (18, 21, and 18%, respectively;  $P = 0.60$ ), but peripheral nerve abnormalities increased (12, 19, and 24%, respectively;  $P = 0.0017$ ). More patients were treated with three or more injections per day (12, 46, and 67%, respectively;  $P < 0.0001$ ) and insulin dose increased (1.08, 1.17, and 1.22 units  $\cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , respectively;  $P < 0.0001$ ), but median HbA<sub>1c</sub> (A1C) was unchanged (8.5, 8.5, and 8.4%, respectively). BMI and height SD score increased: BMI 0.46, 0.67, and 0.79, respectively ( $P < 0.0001$ ), and height  $-0.09$ ,  $0.05$ , and  $0.27$ , respectively ( $P < 0.0001$ ).

**CONCLUSIONS** — Retinopathy and microalbuminuria declined over time in this cohort, but the increased rate of peripheral nerve abnormalities is of concern. Despite intensified management (higher insulin dose and more injections), A1C has not changed and remains well above the recommended targets for adolescents.

*Diabetes Care* 28:1974–1980, 2005

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Received for publication 20 January 2005 and accepted in revised form 5 May 2005.

**Abbreviations:** AER, albumin excretion rate; DCCT, Diabetes Control and Complications Trial; T1, first study period, ranging from 1990 to 1994; T2, second study period, ranging from 1995 to 1998; T3, third study period, ranging from 1999 to 2002.

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

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Management of childhood diabetes has been influenced greatly by the knowledge that intensive management during adolescence reduces the risk of long-term diabetes complications, as seen in the Diabetes Control and Complications Trial (DCCT) (1). Home blood glucose monitoring and measures of glycemic control such as HbA<sub>1c</sub> (A1C) estimations have also changed childhood diabetes treatment over time. A multidisciplinary team provides age-adjusted educational programs along with psychosocial support.

Recognition that screening is important to identify individuals who will benefit from interventions has led to screening programs for adolescents (2,3). Prevention of long-term chronic complications has now become one of the main goals of modern type 1 diabetes treatment in children and adolescents.

In Australia, we initially reported a retinopathy rate of 42% in adolescents (4) and microalbuminuria has been found in 4–20% of children, mostly after the age of 12–15 years (5–7). Although symptomatic neuropathy is uncommon in children with diabetes, previous studies have found a high prevalence of subclinical neurological abnormalities: nerve conduction abnormalities in 51% (8), cardiac autonomic abnormalities in 31% (9), and reduced sensory sensibility in 16% (10). A decline in the cumulative incidence of nephropathy was reported in Linköping, Sweden, in 1994 in individuals diagnosed as children during 1961–1980 (11). This finding was considered by some to apply to only that geographical area because a similar study in Denmark reported an unchanged incidence of diabetic nephropathy in type 1 diabetic patients (12). Later, they reported a reduction in proliferative retinopathy after further follow-up (13), while reductions in nephropathy and retinopathy have also been reported in Denmark (14). To date, a reduction in neuropathy has not been reported.

The aims of the present study were to assess the change in prevalence of microvascular complications, including nerve

Table 1—Characteristics of adolescents with type 1 diabetes in the three time periods

	T1	T2	T3	P
n	257	284	337	—
Sex	123 M, 134 F	137 M, 147 F	153 M, 184 F	0.74
Not treated with CSII	0	0	9	
Year at diagnosis				
1977–1980	46	0	0	
1981–1985	126	49	3	
1986–1990	85	164	77	
1991–1997	0	71	257	
Retinopathy	120/244 (49)	84/268 (31)	77/324 (24)	<0.0001
Clinical retinopathy	29/244 (12)	11/246 (4)	6/308 (2)	<0.0001
AER ≥7.5 μg/min	61/162 (38)	75/247 (30)	75/296 (25)	0.022
Microalbuminuria	11/162 (7)	7/247 (3)	8/296 (3)	0.058
≥1 autonomic nerve abnormality	46/254 (18)	52/246 (21)	31/174 (18)	0.60
≥1 peripheral nerve abnormality	32/257 (12)	47/249 (19)	80/332 (24)	0.0017
Age (years)	14.6 (14.1–16.6)	14.5 (14.0–15.7)	14.6 (14.0–16.1)	0.14
Duration (years)	7.9 (6.2–10.3)	7.2 (6.1–10.0)	7.5 (6.2–10.2)	0.48
A1C (%)	8.6 (7.8–9.6)	8.7 (7.9–9.8)	8.7 (8.0–9.6)	0.30
Median A1C (%)*	8.5 (7.8–9.2)	8.5 (8.0–9.2)	8.4 (7.9–9.0)	0.36
Number of A1C	5 (2–9)	14 (7–21)	17 (11–23)	<0.0001
Mean AER (μg)	6.2 (4.0–10.1)	5.4 (3.8–8.5)	4.5 (3.3–7.7)	0.0003
Height SDS	−0.09 ± 1.02	0.05 ± 0.98	0.27 ± 0.97	<0.0001
Weight (kg)	58.6 (51.0–65.9)	59.5 (52.4–67.8)	63.3 (54.2–72.2)	<0.0001
Weight SDS	0.37 (−0.20 to 0.97)	0.63 (0.10–1.11)	0.85 (0.28–1.44)	<0.0001
BMI SDS	0.46 (−0.03 to 0.93)	0.67 (0.19–1.13)	0.79 (0.22–1.33)	<0.0001
Systolic blood pressure centile	58 (44–82)	73 (55–85)	74 (51–86)	<0.0001
Diastolic blood pressure centile	79 (57–90)	79 (64–89)	79 (60–84)	0.37
Cholesterol (mmol/l)	4.5 (3.8–5.0)	4.3 (3.8–5.0)	4.5 (3.9–5.2)	0.20
Insulin dose/weight	1.08 (0.96–1.28)	1.17 (1.01–1.40)	1.22 (1.03–1.43)	<0.0001
Socioeconomic risk score	0.31 (−0.17 to 0.80)	0.23 (−0.17 to 0.80)	0.36 (−0.07 to 0.94)	0.17
Urban area	158/216 (73)	180/266 (68)	229/329 (70)	0.42
Numbers of injections/day				
1–2	227/257 (88)	149/276 (54)	110/333 (33)	<0.0001
3–5	30/257 (12)	127/276 (46)	223/333 (67)	
Moderately severe hypoglycemia in last 12 months	24/241 (10)	24/253 (9)	21/325 (6)	0.26
Severe hypoglycemia in last 12 months	18/240 (8)	17/251 (7)	28/325 (9)	0.71

Data are n (%), median (interquartile range), or means ± SD. \*Median of all available A1C measurements. CSII, continuous subcutaneous insulin infusion.

function abnormalities, in adolescents from 1990 to 2002 and to investigate their predictors in the post-DCCT era.

## RESEARCH DESIGN AND METHODS

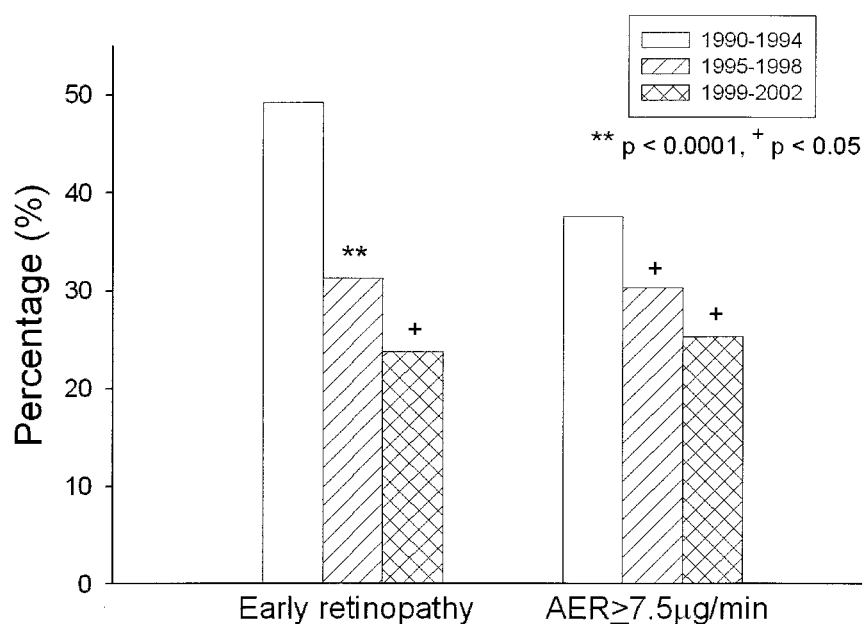
Adolescents aged 12–20 years of age with type 1 diabetes for at least 5 years were assessed at the Children's Hospital at Westmead between 1990 and 2002. Patients were matched for age and duration across the three time periods: 1990–1994 (T1, n = 257), 1995–1998 (T2, n = 284), and 1999–2002 (T3, n = 337). Median age was 14.6 years (interquartile range 14.1–16.2) and median duration was 7.5 years (6.1–10.1) for the total study group. Patients were

diagnosed between the years 1977 and 1989 (T1), 1981 and 1993 (T2), and 1985 and 1997 (T3). Patients and their parents gave informed consent for the results of their complication assessment to be analyzed, and the study was approved by the ethics committee of the Children's Hospital at Westmead.

### Complication assessment

Assessment of complications was undertaken during a 2-h clinic visit, and patients were referred by the caring physician. Retinopathy was assessed by seven-field stereoscopic fundal photography using a Topcon Fundas camera (TRC 50-VT; Tokyo Optical) after dilatation of

the pupils with 1% cyclopentolate and 2.5% phenylephrine. Grading was performed by the same ophthalmologist (S.H.) according to modified Airlie House classification (15). Retinal slides were regraded for 39 randomly selected patients (78 individual eyes) from the period 2001 to 2002 and 45 randomly selected patients (90 individual eyes) from 1990 to 1994. Agreement between the two gradings, using a weighted κ score, was 0.81 (very good agreement). Early retinopathy was defined as at least one microaneurysm or hemorrhage (grade 21/10 or higher) in one eye. Clinical retinopathy was defined as at least one microaneurysm and one hemorrhage in one eye and at least



**Figure 1**—Reduction in frequency of retinopathy and AER  $\geq 7.5$   $\mu\text{g}/\text{min}$  over three time periods.

one microaneurysm or hemorrhage in the other eye (grade 31/21 or higher).

Albumin excretion rate (AER) was determined from three consecutive timed overnight urine collections. Albumin was measured using a polyclonal radioimmunoassay (Pharmacia RIA, Beckman Coulter, Australia) from 1990 to March 2000. The laboratory changed to nephelometry using the IMMAGE analyzer thereafter (IMMAGE = 0.8734, radioimmunoassay value  $-0.501$ ,  $R^2 = 0.98$ ). Early elevation of AER was defined as mean AER  $\geq 7.5$   $\mu\text{g}/\text{min}$ . This cutoff was selected because the 95th percentile was 7.2  $\mu\text{g}/\text{min}$  in 690 nondiabetic Australian children aged  $11.5 \pm 3.38$  years (16) and 7.6  $\mu\text{g}/\text{min}$  in 41 nondiabetic Americans aged 13–22 years (17). Microalbuminuria was defined as AER  $\geq 20$   $\mu\text{g}/\text{min}$  in at least two of the three samples.

Autonomic nerve function was assessed by measuring heart rate variation during deep breathing, standing from a lying position (30/15 ratio), and the change in systolic blood pressure on standing from a lying position (Autocast Programme; Unived Technologies, Edinburgh, U.K.), as previously described (18). Peripheral nerve function was assessed by thermal threshold testing for hot and cold at the left foot (Thermal Threshold Tester; Medelec, Old Woking, Surrey, U.K.) and vibration threshold at the left medial malleolus and left great toe

(Biothesiometer; Biomedical Instruments, Newbury, OH). Reference ranges were previously determined in nondiabetic adolescents using the 5th centile for autonomic and 95th centile for peripheral nerve tests (18).

Glycemic control was assessed by GHb colorimetrically before February 1994 (19) and A1C by high-performance liquid chromatography (Diamat Bio-Rad; normal range 4–6%) subsequently at complication assessment. GHb values were converted to A1C (18) (Diamat =  $1.9088 + 0.0043 \times \text{GHb}$ ,  $R^2 = 0.85$ ). DCA 2000 analyzer values were included at interim clinic visits from 1994 (Diamat =  $1.0766 \times \text{DCA 2000} - 0.0871$ ,  $R^2 = 0.9206$ ), and all available values for glycated hemoglobin were included to calculate the individual's median A1C.

Urban/rural status was determined by postcode using data from the Australian Bureau of Statistics (20). A locality-based social disadvantage risk score was used as a measure of social disadvantage (21). The scale was derived from nine risk indicators (unemployment, long-term unemployment, unskilled workers, leaving school before 15 years of age, low income, child abuse, low birth weight, court convictions, and emergency assistance) for NSW Australia postal codes. The scale was developed to enable estimates of the degree of inequality and diminished life opportunities experienced by people re-

siding in neighborhoods across NSW. The score ranged from  $-5.21484$  (most social disadvantage) to  $1.83241$  (least social disadvantage).

Height and weight were measured using a Harpenden stadiometer and electronic weighing scale, respectively, and BMI was calculated ( $\text{kg}/\text{m}^2$ ) at the time of complication assessment. Blood pressure was measured in the seated position with a sphygmomanometer after 5 min of rest using the appropriate cuff size. The cuff size was selected ensuring that the bladder spanned the circumference of the arm and covered at least 75% of the upper arm without obscuring the antecubital fossa. Age- and sex-related centiles for systolic and diastolic blood pressure were calculated using published standards (22). Pubertal staging was assessed by the endocrinologist.

Number of injections, total daily insulin doses, and number of severe (unconsciousness or seizures) and moderately severe (requiring assistance for treatment) hypoglycemic episodes in the previous 12 months were recorded.

### Statistical analysis

The Kruskal-Wallis test was used to compare continuous variables across the three groups. For categorical variables, associations with the three time periods were assessed by a  $\chi^2$  test. Post hoc comparisons were made by logistic regression. Risk factors associated with complications were determined by multiple logistic regression.

**RESULTS**— Results are given comparing the three time periods (Table 1), unless otherwise stated.

### Retinopathy

Early retinopathy declined significantly over the study period, and the three time points were significantly different from each other (Fig. 1). Clinical retinopathy also declined; the prevalence for T2 and T3 combined was significantly lower than in T1 (Fig. 2A).

### Albumin excretion

AER  $\geq 7.5$   $\mu\text{g}/\text{min}$  declined, and the three time points were significantly different from each other (Fig. 1). Microalbuminuria also declined; the prevalence for T2 and T3 combined was significantly lower than that for T1 (Fig. 2A).

### Nerve function tests

The prevalence of autonomic nerve function abnormalities was unchanged, but peripheral nerve abnormalities increased. The prevalence for T2 and T3 combined was significantly higher than that for T1 (Fig. 2B).

### Insulin therapy and glycemic control

Glycemic control was unchanged over the three study periods, based on the A1C on the day of assessment. The individual median A1C (calculated from all available A1C values up to and including the complication assessment) was also unchanged over time, but the median number of A1C measurements increased. An increasing proportion of patients were treated with three or more injections per day, and the insulin dose (per kilogram body weight) increased. There was no change in reported moderately severe hypoglycemia or severe hypoglycemia (Table 1).

### Macrovascular risk factors

Median systolic blood pressure centile increased, but diastolic blood pressure centile was unchanged. Cholesterol levels were unchanged over the three time periods.

### Growth

BMI and height SD score increased significantly over time.

### Demographic characteristics

There was no significant change in socioeconomic risk score or proportion of patients from urban/rural areas over time.

### Multiple logistic regression

Retinopathy was associated with longer diabetes duration, higher median A1C, and earlier time period (T1). Associated risk factors for  $AER \geq 7.5 \mu\text{g}/\text{min}$  were later pubertal staging, higher cholesterol, and earlier time periods (T1 and T2). Microalbuminuria was associated with later pubertal staging, female sex, and higher diastolic blood pressure centile. Peripheral nerve function abnormalities were associated with greater height SD score, male sex, and later time periods (T2 and T3) (Table 2).

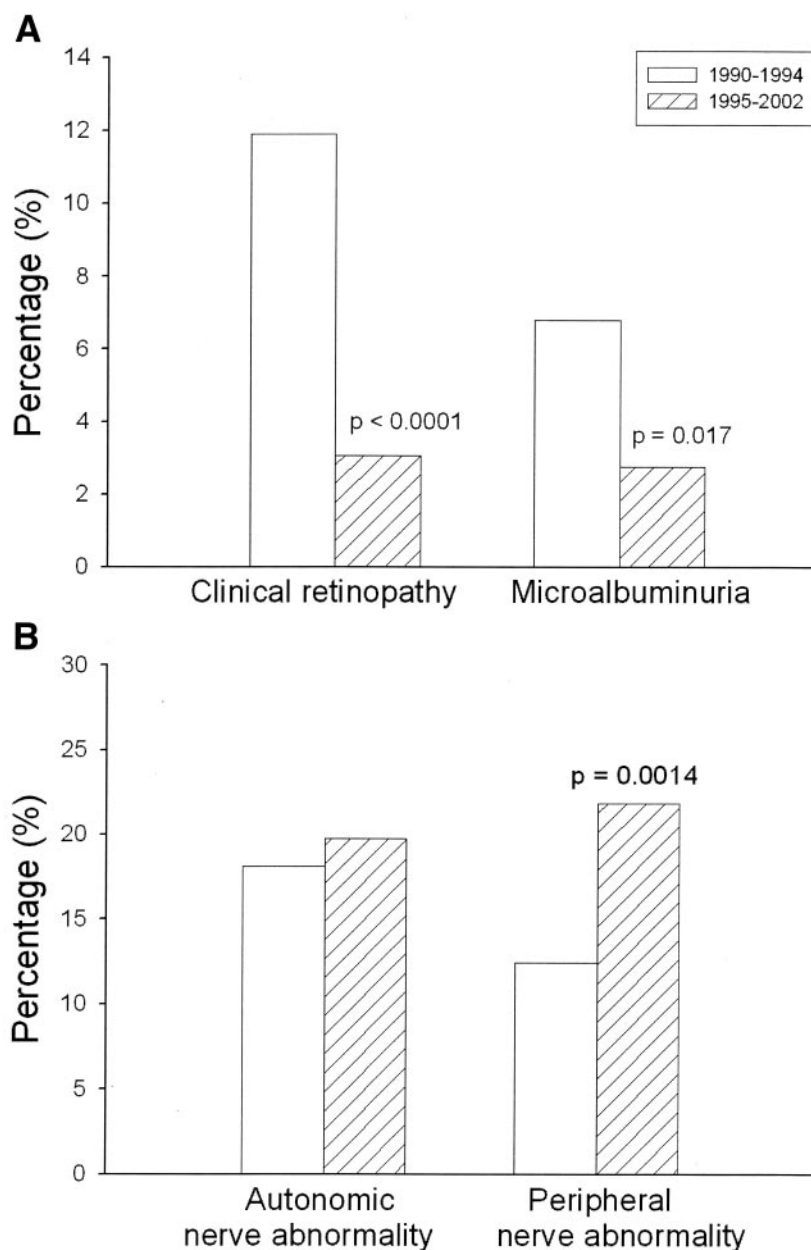
**CONCLUSIONS**— In this large cohort of adolescents, prevalence of early and clinical retinopathy and early elevation of AER have declined in the post-DCCT era. An unexpected finding was an increase in the prevalence of peripheral

nerve function abnormalities over time. There was no documented change in A1C or hypoglycemia.

Because microalbuminuria was so infrequent across the study periods, there was unsatisfactory power (55%) to be certain of its decline. Hence, we have also used a lower surrogate marker for renal disease, namely  $AER \geq 7.5 \mu\text{g}/\text{min}$ , which we have previously shown to have the same risk associations as microalbuminuria and similar median time to develop as “early retinopathy” (23). Longitudinal

studies have shown that patients with early elevation of AER (>95th percentile) are at risk of progression (24,25).

Over the study period, an intensification of insulin therapy was found, as measured by increase in number of injections and insulin doses, but an improvement in A1C was not found. All patients in the study had access to home blood glucose monitoring almost since diagnosis (introduced in NSW in 1978). We expected an improvement in A1C over time, but the median A1C was 8.5% for the entire study



**Figure 2**—Change in frequency in clinical retinopathy and microalbuminuria (A) and autonomic and peripheral nerve abnormalities (B).

Table 2—Results of logistic regression analysis for risk factors of microvascular complications

	Predictor	Odds ratio (95% CI)	P
Retinopathy	Age at diagnosis	1.20 (1.07–1.33)	0.0014
	Duration	1.34 (1.18–1.52)	<0.0001
	Median A1C	1.52 (1.29–1.80)	<0.0001
	Height SDS	0.78 (0.66–0.93)	0.0048
	T1	2.46 (1.74–3.47)	<0.0001
	Socioeconomic risk score	0.79 (0.64–0.99)	0.038
Clinical retinopathy	Age at diagnosis	1.27 (1.02–1.58)	0.035
	Duration	1.54 (1.20–1.98)	0.0006
	Median A1C	2.32 (1.69–3.19)	<0.0001
	BMI SDS	1.90 (1.16–3.11)	0.011
	T1	5.66 (2.85–11.26)	<0.0001
AER $\geq 7.5$ $\mu\text{g}/\text{min}$	Pubertal stage 3–5	2.85 (1.08–7.51)	0.035
	Cholesterol	1.27 (1.002–1.61)	0.048
	T3	0.51 (0.32–0.83)	0.0063
Microalbuminuria	Pubertal stage 5	3.20 (1.06–9.67)	0.040
	Diastolic blood pressure centile	1.04 (1.01–1.07)	0.010
Any autonomic nerve abnormality	Male	0.21 (0.06–0.71)	0.013
	None		
Any peripheral nerve abnormality	Male	1.93 (1.33–2.78)	0.0005
	Height SDS	1.50 (1.24–1.81)	<0.0001
	T1	0.54 (0.35–0.84)	0.0066
	Moderately severe hypoglycemia	0.42 (0.18–0.96)	0.040

population, consistent with our recent population-based audit of glycemic control (26). Although it is clearly established that multiple injection regimens are superior to simpler regimens in adults with type 1 diabetes (27), more injections may not be associated with lower A1C in adolescent age-groups (28). A1C, currently the gold standard for assessing glycemic control, does not provide a measure of the magnitude or frequency of fluctuations in blood glucose throughout the day. Indeed, researchers have more recently emphasized postprandial glycemic spikes as contributors to diabetes complications (29), which can go undetected if only A1C values are assessed. In keeping with this hypothesis, the intensively treated DCCT patients had a significantly lower risk of retinopathy progression compared with the conventionally treated group for the same updated mean of A1C (30). This is consistent with our finding of reduced retinopathy prevalence with more injections but the same measured A1C. It is possible that the later cohorts in the present study, treated with more injections

and higher insulin doses, had fewer glucose excursions that were not detected by the steady A1C. It is of note that only nine subjects were treated with continuous subcutaneous insulin infusion in the study period of 1999–2002.

Glycemic control may have been unevenly recorded in the earlier years of our database, as shown by fewer A1C records in the earlier periods. It is of note that, for the colorimetric method used in the earlier period, both the intra-assay and inter-assay variations were much wider compared with those of Diamat used in the later study periods (intra-assay variation 2.6 vs. 0.38%, interassay variation 6.3 vs. 0.75%). This result may have given a false impression of overall glycemic control of the participants in the earlier time period. Despite no change in A1C over time for the entire cohort, the median A1C was significantly associated with risk of retinopathy in multiple logistic regression analysis.

Despite a reduction in retinopathy and AER, we have documented an increase in abnormalities in peripheral

nerve function measured by quantitative sensory tests (vibration and thermal threshold). Vibration discrimination tests large myelinated fibers, and temperature discrimination tests small unmyelinated and thinly myelinated fibers. These tests are independent of the observer/operator but are limited by the subject's attention, motivation, and cooperation. Any variation, however, is unlikely to have contributed systematically to the increase in abnormalities over time. Furthermore, abnormal biothesiometry on diabetic children correlate with nerve conduction abnormalities (31). Although nerve conduction is the most sensitive for detecting peripheral nerve function abnormalities, only vibration and thermal abnormalities have been shown to predict future foot ulceration (32,33).

The increase in peripheral nerve function abnormalities paralleled an increase in height and BMI over the study period, and greater height was significantly associated with peripheral nerve function abnormality. Increasing height was associated with peripheral neuropathy in the EURODIAB IDDM Complications Study (34) and clinical neuropathy in the DCCT baseline study (35). A unifying hypothesis for our discordant finding of an increase in peripheral nerve abnormalities with a reduction in early renal and retinal disease would be an increased rate of hypoglycemia, because the cerebral and peripheral nervous systems are adversely affected by hypoglycemia (36), whereas the blood vessels of the retina and nephron are not. Although patient recall of hypoglycemia did not change over time, milder hypoglycemia may have contributed to our findings. Along with median A1C, age at diagnosis and duration were associated with risk of retinopathy. Most pediatric studies have found duration to be the major factor for retinopathy (4,37), but the effect is nonlinear before onset of puberty for retinopathy and for elevation of AER (23). We found higher pubertal stage to be a risk factor for AER  $\geq 7.5$   $\mu\text{g}/\text{min}$  and microalbuminuria and cholesterol for AER  $\geq 7.5$   $\mu\text{g}/\text{min}$ . The later stages of puberty with higher sex steroid levels may magnify the glycemic changes. In the present study, male sex had a lower risk of microalbuminuria, consistent with findings in other studies (38,39), and may be due to boys' later onset of puberty and later growth spurt. We confirmed higher diastolic blood

pressure to be an associated risk factor of microalbuminuria, as previously found (40). Diet plays a major role in the overall management of type 1 diabetes. Recent trends in flexible dietary instruction based on the USDA food pyramid, with emphasis on low-glycemic index foods, has been shown to improve glycemic control in children with type 1 diabetes (41). The use of low-glycemic index foods reduces postprandial hyperglycemia, which in turn may affect carbohydrate and lipid metabolism and renal function (42). Dietary data were not included in the present study, but dietary changes may have contributed to the reduction in microvascular complications, despite no change in clinic A1C. Smoking is a risk factor for microvascular complications (16,43). Smoking status was not recorded in the present study, but it is of note that the prevalence of smoking among Australian adolescents has declined (44).

Limitations of this study include its cross-sectional design and that the cohorts were clinic rather than population based. A strength of the study was its large sample size, and the three groups were closely comparable in age and duration of diabetes. They were also comparable in socioeconomic risk score and urban/rural status and represent the typical population of adolescents with type 1 diabetes in our state (26). These points strongly argue against the possibility of selection bias toward later study periods. It is possible that individuals with better adherence to diabetes routines are more likely to attend recommended screening, so adolescents not attending clinical care may not have experienced the same decline in complications.

In conclusion, there appears to be a declining prevalence of microvascular complications over time in this non-population-based cohort. Although A1C was not significantly different in the three groups, there was evidence of intensified management, specifically an increase in insulin dose and number of injections. The increase in nerve function abnormalities may be due to the observed increased height over time, but these findings indicate that ongoing review of nerve function in adolescents is required.

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