Continued Reduction in the Prevalence of Retinopathy in Adolescents With Type 1 Diabetes

Role of insulin therapy and glycemic control

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OBJECTIVE—To examine trends in microvascular complications in adolescents with type 1 diabetes between 1990 and 2009 in Sydney, Australia.

RESEARCH DESIGN AND METHODS—We used analysis of complications in 1,604 adolescents (54% female, aged 12–20 years, median duration 8.6 years), stratified by four time periods using Generalized Estimation Equations as follows: T1 (1990–1994), T2 (1995–1999), T3 (2000–2004), and T4 (2005–2009). Early retinopathy was detected using seven-field fundal photography, albumin excretion rate (AER) using timed overnight urine collections, and albumin-to-creatinine ratio (ACR) and peripheral nerve function using thermal and vibration threshold.

RESULTS—Retinopathy declined (53, 38, 23, and 12%; $P < 0.001$), as did borderline elevation of AER/ACR (45, 30, 26, and 30%; $P < 0.001$) and microalbuminuria (8, 4, 3, and 3%; $P = 0.006$). Multiple daily injections (MDI)/continuous subcutaneous insulin infusion (CSII) use increased (17, 54, 75, and 88%; $P < 0.001$), median HbA_{1c} decreased (9.1, 8.9, 8.5, and 8.5%; $P < 0.001$), and severe hypoglycemia was unchanged (6, 8, 10, and 7%; $P = 0.272$). Retinopathy was associated with diabetes duration (odds ratio [OR] 1.12 [95% CI 1.08–1.17]), age (1.13 [1.06–1.20]), HbA_{1c} (1.16 [1.08–1.25]), systolic blood pressure (BP) SDS (1.31 [1.16–1.48]), socioeconomic disadvantage (1.42 [1.04–1.95]), and 1 to 2 injections per day (vs. MDI/CSII; 1.35 [1.05–1.73]); borderline AER/ACR with male sex (1.32 [1.02–1.70]), age (1.19 [1.12–1.26]), HbA_{1c} (1.18 [1.08–1.29]), weight SDS (1.31 [1.21–1.53]), insulin dose per kilograms (1.64 [1.13–2.39]), 1 to 2 injections per day (1.41 [1.08–1.84]), and socioeconomic disadvantage (1.68 [1.23–2.31]); and microalbuminuria with age (1.14 [1.01–1.29]), HbA_{1c} (1.20 [1.05–1.37]), diastolic BP SDS (1.76 [1.26–2.46]), and 1 to 2 injections per day (1.95 [1.11–3.41]).

CONCLUSIONS—The decline in retinopathy supports contemporary guidelines that recommend lower glycemic targets and use of MDI/CSII in children and adolescents with type 1 diabetes.

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Before the findings of the Diabetes Control and Complications Trial (DCCT) (1), retinopathy prevalence in adolescents with diabetes was approximately 41 to 42% in both Australia and the U.S. (2,3) and slightly higher in some European centers (46%) (4), whereas microalbuminuria rates ranged between 4 and 20% (5,6). Post-DCCT, intensive management was recommended but glycemic targets were difficult to achieve in young people, with median hemoglobin A_{1c} (HbA_{1c}) of clinic patients often above the recommended glycemic target of 7.5% (7,8). Nonetheless, there is evidence for a decreasing trend in some complications. We have reported previously a reduction in retinopathy and borderline elevation of albumin excretion rate (AER)/albumin-to-creatinine ratio (ACR; a surrogate marker for microalbuminuria) from 1990 to 2002, whereas microalbuminuria declined and then reached a plateau (7). In contrast, others have found a steady rate of microalbuminuria since 1986 (9).

Since our previous report (7), the use of insulin analogs has increased, along with greater use of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) (10). Although the DCCT demonstrated a reduced risk of microvascular complications in adults and adolescents treated with intensive management, which included a package of multidisciplinary care and frequent contact with the diabetes team in addition to MDI or CSII, the association between intensive treatment regimens (CSII or MDI) and improved glycemic control is less clear in children (11,12). Furthermore, there is no evidence demonstrating a reduced risk of complications in children treated with CSII or MDI versus 1 to 2 injections per day. This may reflect previous higher glycemic targets for younger children as a result of the increased risk of hypoglycemia.

In this study of 1,604 adolescents with type 1 diabetes, we examined trends in the prevalence of microvascular complications from 1990 to 2009. We specifically sought to examine the association between time period and complication outcomes (retinopathy, microalbuminuria, neuropathy), in addition to recognized risk factors (HbA_{1c}, diabetes duration, blood pressure), socioeconomic disadvantage, and treatment regimens (MDI and CSII).

RESEARCH DESIGN AND METHODS

Study population

The study population consisted of 1,604 patients with type 1 diabetes seen at the Diabetes Complications Assessment Service

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at The Children's Hospital at Westmead from 1990 to 2009. Inclusion criteria for the study were age between 12 and 20 years and diabetes duration of at least 5 years. Patients (and their families if family members were aged <18 years) provided informed consent for the results of their complications assessment to be analyzed. The study was approved by The Children's Hospital at Westmead Ethics Committee.

Complications assessment

Patients were assessed during a 2-h clinic visit, as described previously (7). Retinopathy was detected using stereoscopic fundal photography of seven fields, and the IMAGEnet2000Lite system was used to digitalize images. The photographs were graded by the same ophthalmologist according to the modified Airlie House classification of diabetic retinopathy (2).

Microalbuminuria was assessed by measurement of mean AER on three consecutive timed overnight urine collections or mean ACR on three morning urine samples. Albumin was measured using a polyclonal radioimmunoassay (Pharmacia RIA; Beckman Coulter Australia). Borderline elevation of AER was defined as AER ≥7.5 μg/min in at least two of the three timed overnight urine collections or by a mean ACR ≥1.0 mg/mmol (males) and ≥1.4 mg/mmol (females). These cutoffs determined as the 95th percentile were 7.2 μg/min in 690 nondiabetic Australian children aged 11.5 ± 3.38 years (13). Microalbuminuria was defined as AER ≥20 μg/min in at least two of the three timed overnight urine collections or by a mean ACR ≥2.8 mg/mmol (male) and ≥4.1 mg/mmol (female) (T.W. Jones, personal communication). There were two changes in assays between 1991 and 2009. Between 1991 and 2000, Pharmacia Radioimmunoassay (Beckman Coulter Australia) was used, before using Immage immunoassay (Beckman Coulter Australia) from 2000 to 2003 and then Immulite immunoassay (Siemens Healthcare). Regression equations for albumin had high correlation (R^2 = 0.98), with *y*-intercept of −0.5 and −0.56 mg/L. Assay coefficient of variation for albumin is 5.9% (range 7.2–9.1 mg) and 4.2% (range 50.6–59.9 mg).

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 Instrument, Newbury, OH) (7,14). Peripheral nerve abnormalities were defined as less than 5% of the normal range in a nondiabetic adolescent control group tested previously in our laboratory (15). Because our nerve testing equipment changed in 2006, we have only included data collected before this time. Data were adjusted for height.

Glycemic control was assessed by GHb colorimetrically before February 1994 (16) and afterward by measurement of HbA_{1c} using the Bio-Rad Diamat analyzer (Bio-Rad, Hercules, CA). GHb values were converted to A1C (15) (Diamat = 1.9088 + 0.0043 × GHb; R^2 = 0.85). DCA 2000 analyzer values were included at interim clinic visits from 1994 (Diamat = 1.0766 × DCA 2000 − 0.0871; R^2 = 0.9206), and all available values for glycated hemoglobin were included to calculate the individual's median A1C. The nondiabetic range for HbA_{1c} is 4–6%. The current target of <7.5% for young people with type 1 diabetes was used to define the group with "raised HbA_{1c}."

Height and weight were measured, and BMI was calculated as kilograms per squared meters. BMI *z* scores were calculated using the 2000 Centers for Disease Control (CDC) reference standards (17). Systolic and diastolic blood pressure (SBP and DBP) *z* scores for age and sex were determined using the U.S. Task Force Report (18). Cholesterol was measured using a Beckman CX5 (1990–1999), using a Dimension RXL (2000–2005), and using a Vitros analyzer (Ortho Clinical Diagnostics) from 2005. High total cholesterol was defined as >5.2 mmol/L.

Socioeconomic status was classified using a postcode-based system according to the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) database (19). The scale was used to classify participants into a socioeconomically disadvantaged group (deciles 1–3) and a socioeconomically advantaged group (deciles 4–10).

Number of injections per day, use of MDI/CSII, total insulin dose per kilgrams per day, and the number of severe episodes of hypoglycemia (defined as unconsciousness or seizures) in the past 12 months were recorded as reported by the patients or their parents. Tanner pubertal staging was based on assessment by the clinician.

Statistical analysis

Summary statistics are reported as mean ± SD if normally distributed or median and interquartile range (IQR) for skewed data. Participants were stratified according to time periods: 1990–1994 (T1), 1995–1999 (T2), 2000–2004 (T3), and 2005–2009 (T4). For patients seen more than once during a time period, only their last visit was included in the analysis. Continuous parametric data were compared across the four time periods using ANOVA, and skewed data were compared using the Kruskal-Wallis test. χ^2 Tests were used to compare categorical data across these four time periods.

Generalized Estimating Equations (GEE) were used to examine factors associated with the complication outcomes (retinopathy, borderline elevation of AER/ACR, microalbuminuria, and peripheral nerve abnormalities), while taking into account multiple visits by individual patients. Explanatory variables included in the models were sex, age, age at diagnosis, duration of disease, pubertal stage (comparing pubertal stage 1 to 2 to 3–5), HbA_{1c}, height SDS, weight SDS, BMI SDS, cholesterol, SBP SDS, DBP SDS, MDI/CSII use (compared with 1 to 2 injections per day), insulin dose per kilograms per day time period (with T1 as the reference group), and socioeconomic disadvantage (SEIFA; comparing socioeconomic deciles 1–3 to 4–7). Because of significant collinearity between time period and use of MDI/CSII, two multivariate logistic regression models were examined. The first model included time period and explanatory variables with $P < 0.25$ in univariate analysis, and the second model included use of MDI/CSII versus 1 to 2 injections per day and explanatory variables with $P < 0.25$ in univariate analysis.

RESULTS—Overall 1,604 patients (54% female) met the inclusion criteria, and results from 2,030 complications assessments were included in the analysis. Therefore, some patients were assessed in more than one time period. The median age at last assessment was 16.2 years (IQR 14.5–17.6), and median duration of diabetes was 8.6 years (IQR 6.6–11.4). Patient characteristics, stratified by time period, are shown in Table 1. Glycemic control improved over time, with HbA_{1c} remaining steady in the last two time periods. The proportion of patients treated with MDI or CSII increased over time; in particular the use of CSIIs increased from 0% in T1 and T2, 4% in T3, and 22% in T4. Insulin dose per kilgrams per day increased across the first three time periods

Table 1—*Patients' characteristics and complication rates in adolescents with type 1 diabetes stratified by time period*

	T1 (1990–1994)	T2 (1995–1999)	T3 (2000–2004)	T4 (2005–2009)	*P* value
Characteristics					
Number	342	517	604	567	—
Sex (male, %)	163 (48)	243 (47)	271 (45)	261 (46)	0.834
Age (years)	15.9 (14.2–17.6)	16.1 (14.6–17.6)	16.1 (14.5–17.7)	16.4 (14.9–17.6)	0.04
Duration (years)	8.6 (6.4–11.3)	8.4 (6.3–11.3)	8.5 (6.6–11.4)	8.9 (7.0–11.5)	0.119
HbA_{1c} (%)	9.1 (8.0–10.1)	8.9 (7.9–9.9)	8.5 (7.7–9.4)	8.5 (7.6–9.5)	<0.001
Number of injections/day					
1 to 2	280/338 (83)	232/507 (46)	151/594 (25)	68/559 (12)	<0.001
3+ or CSII	58/338 (17)	275/507 (54)	443/594 (75)	491/559 (88)	<0.001
Insulin dose (units/kg/day)	1.07 (0.92–1.26)	1.15 (0.97–1.35)	1.16 (0.98–1.39)	1.08 (0.03–1.31)	<0.001
Height SDS	−0.03 ± 0.99	0.14 ± 0.97	0.24 ± 0.99	0.17 ± 1.02	0.01
Weight SDS	0.46 (−0.15 to 0.95)	0.75 (0.21–1.20)	0.82 (0.27–1.35)	0.84 (0.30–1.35)	<0.001
BMI SDS	0.47 (−0.01 to 0.91)	0.69 (0.17–1.18)	0.80 (0.27–1.27)	0.82 (0.27–1.28)	<0.001
Cholesterol (mmol/L)	4.4 (3.8–5)	4.4 (3.8–5.1)	4.4 (3.8–5)	4.3 (3.8–4.9)	0.795
SBP SDS	0.22 (−0.17 to 0.92)	0.56 (0.09–1.03)	0.01 (−0.7 to 0.91)	−0.38 (−0.92 to 0.22)	<0.001
DBP SDS	0.76 (0.27–1.31)	0.63 (0.18–1.08)	0.56 (−0.14 to 0.94)	0.25 (−0.21 to 0.84)	<0.001
Socioeconomic disadvantage	75/310 (24)	127/500 (25)	88/602 (15)	59/560 (11)	<0.001
Complications					
Retinopathy	173/325 (53)	183/481 (38)	134/581 (23)	64/556 (12)	<0.001
Borderline AER/ACR*	102/225 (45)	128/429 (30)	137/526 (26)	127/425 (30)	<0.001
Microalbuminuria	18/215 (8)	18/403 (4)	15/503 (3)	14/399 (3)	0.006
≥1 Peripheral nerve abnormality†	25/339 (7)	61/452 (14)	85/600 (14)	10/71 (14)	0.016
Severe hypoglycemia in past 12 months	20/323 (6)	36/460 (8)	55/578 (10)	39/551 (7)	0.272

Data are *n* (%), mean ± SD, or median (IQR). *Borderline AER/ACR is defined by an AER ≥7.5 μg/min, or an ACR ≥1.4 mg/mmol in females and ≥1.0 mg/mmol in males; †datum has been adjusted for height.

but declined in T4. BMI and weight SDS both increased significantly over time, and there was a significant increase in socioeconomic status over the four time periods. The frequency of severe hypoglycemia in the previous 12 months remained steady over time. When only a single visit from each patient was included in the analysis (1,604 visits), the significant trends over time remained.

The prevalence of retinopathy decreased significantly over time, whereas borderline elevation of AER/ACR declined over the first three time periods, before reaching a plateau in T4. Microalbuminuria decreased from T1 to T2, before reaching a plateau in T3 and T4. The prevalence of peripheral nerve abnormalities increased from T1 to T3 and remained steady in T4.

In the most recent time period, 22% were treated with CSII and 65% were treated with MDI. There was some evidence that there was a reduced risk of retinopathy in those treated with CSII versus MDI (OR 0.52 [95% CI 0.26–1.06]); however, this did not reach statistical significance ($P = 0.07$). There was a reduced risk of nerve abnormalities in patients treated with CSII versus MDI (0.63 [0.40–1.00]; $P = 0.05$).

Multivariate analysis of complication outcomes

Retinopathy was associated with older age at diagnosis, disease duration, higher HbA_{1c}, lower height SDS, higher SPB SDS, 1 to 2 injections per day (vs. MDI/CSII), and socioeconomic disadvantage (Table 2). Trends in retinopathy rates, use of MDI/CSII, and HbA_{1c} are shown in Fig. 1.

Both borderline elevation of AER/ACR and microalbuminuria were associated with increasing age, higher HbA_{1c}, and 1 to 2 injections per day versus MDI/CSII use (Table 2). Borderline elevation of AER/ACR was also associated with male sex, greater weight SDS, higher insulin dose per kilogram, and socioeconomic disadvantage. Microalbuminuria was also associated with higher DBP SDS (Table 2).

The only variable associated with peripheral nerve abnormalities was use of 1 to 2 injections per day versus MDI/CSII (Table 2). Pubertal stage was not associated with any of the complication outcomes.

CONCLUSIONS—In this 20-year study of 1,604 adolescents with type 1 diabetes, the prevalence of retinopathy has continued to decrease in parallel with a decline in HbA_{1c} and intensification of management. In contrast, there has been a recent plateau in the prevalence of microalbuminuria and peripheral nerve abnormalities. Severe hypoglycemia has remained unchanged. Although this was not an interventional study, we have confirmed a contemporary association among intensive management, improved glycemic control, and lower risk of retinopathy, more than 20 years after the DCCT was performed (1). Our findings provide some reassurance for lower glycemic targets and increased use of MDI and CSII in children and adolescents with type 1 diabetes.

The strengths of this study include the sample size, with 1,604 adolescents and 2,030 assessments over 20 years. This was a free-living observational trial, and patient characteristics (diabetes duration, demographics) were comparable over the four time periods. It is a well-described population, with comprehensive data collected at each visit. All patients were assessed at one center, and there were few changes in the complications assessment methods throughout the study period, with a small number of changes in assessment personnel and the

Table 2—*Generalized estimation equations for factors associated with microvascular complications in adolescents with type 1 diabetes*

	Univariate model		Multivariate model	
Outcome and factor	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Retinopathy				
Duration	1.15 (1.11–1.19)	<0.001	1.12 (1.08–1.17)	<0.001
Age	1.18 (1.12–1.24)	0.001	1.13 (1.06–1.20)	<0.001
HbA_{1c}	1.19 (1.11–1.27)	<0.001	1.16 (1.08–1.25)	<0.001
Height SDS	0.78 (0.70–0.88)	<0.001	0.82 (0.73–0.93)	0.002
SBP SDS	1.33 (1.18–1.49)	<0.001	1.31 (1.16–1.48)	<0.001
1 to 2 injections (vs. MDI/CSII)	1.36 (1.07–1.73)	0.011	1.35 (1.05–1.73)	0.021
SES disadvantaged group	1.44 (1.08–1.92)	0.008	1.42 (1.04–1.95)	0.027
Borderline elevation AER/ACR				
Male	1.25 (0.98–1.61)	<0.001	1.32 (1.02–1.70)	0.033
Age	1.11 (1.05–1.17)	<0.001	1.19 (1.12–1.26)	<0.001
HbA_{1c}	1.18 (1.09–1.28)	<0.001	1.18 (1.08–1.29)	<0.001
Weight SDS	1.20 (1.03–1.39)	<0.001	1.31 (1.12–1.53)	0.001
1 to 2 injections (vs. MDI/CSII)	1.25 (0.97–1.61)	0.088	1.41 (1.08–1.84)	0.01
Insulin dose	1.45 (1.03–2.05)	0.034	1.64 (1.13–2.39)	0.010
SES disadvantaged group	1.60 (1.18–2.19)	0.003	1.68 (1.23–2.31)	0.011
Microalbuminuria				
Age	1.13 (1.00–1.26)	0.044	1.14 (1.01–1.29)	0.006
HbA_{1c}	1.23 (1.06–1.43)	0.008	1.20 (1.05–1.37)	0.005
DBP SDS	1.82 (1.28–2.58)	0.001	1.76 (1.26–2.46)	0.001
1 to 2 injections (vs. MDI/CSII)	1.76 (0.99–3.15)	0.056	1.95 (1.11–3.41)	0.027
Peripheral nerve abnormality				
1 to 2 injections (vs. MDI/CSII)	0.71 (0.54–0.92)	0.011		

same retinal specialist grading the retinal images.

There are several factors that may influence the interpretation of our findings. In our last report (7), patients were matched according to age across time periods, whereas in the current study, there was a small increase in age across the four time periods (from 15.9 to 16.4 years). However, given the recognized association between retinopathy and age, this may be expected to bias the results toward a higher prevalence of retinopathy recently, rather than the reduction that we observed (2). The inclusion of more than one visit for some patients, although in different time periods, may have introduced response bias. However, there was no difference in trends over time (Table 1) when only one assessment per patient was analyzed. Multivariate analysis of factors associated with microalbuminuria was limited by the low prevalence of microalbuminuria, with only 65 cases over 20 years (4%). We therefore used a surrogate measure, borderline elevation of AER/ACR, which has many of the same risk associations as microalbuminuria (20). Over the time course of the observation period the albumin assay methods changed in the 5th year of T2 and during T3. This is unlikely to have biased our results, since we have observed a plateau in AER elevation over this period with reduction only between T1 and T2.

Retinopathy was found in approximately half of adolescents with type 1 diabetes after a median duration of ~9 years in the early 1990s, compared with only 12% in recent years (Fig. 1). It is of interest that in subgroup analysis of patients treated only with intensive management in T4, there was some evidence for reduced risk for retinopathy in those treated with CSII compared with MDI. Given there was no difference in A1C between groups, we hypothesize that reduced glycemic variability may have contributed to this difference. Although others have found a similar trend in decreasing HbA_{1c} with time (21), to the best of our knowledge there are no studies demonstrating a specific benefit of CSII over MDI on complications in adolescents. There are now more patients than ever reaching the recommended HbA_{1c} target of 7.5%. The prevalence of complications in these patients is lower than in those who did not reach the target range, supporting this as the target.

Other potential modulators of the reduction in retinopathy should be considered. Earlier diagnosis of diabetes in more recent years could result in better preservation of C-peptide reserve and hence potentially less glycemic variability. We were unable to assess this possibility because C-peptide was not available in the early time periods; however, there is no evidence for a reduction in diabetes ketoacidosis at presentation over the 20 years. Another potential cause for reduction in retinopathy could be concurrent use of other medications, but very few of the adolescents were taking antihypertensive or lipid modulators (<1%). It is possible that the health message of smoking has resulted in a lower rate of smoking, but we were unable to objectively measure this (13). It remains most likely that the improvement is a result of the demonstrated glycemic control. This analysis could not inform us of whether the current glycemic target of 7.5% is optimal, since there were too few participants meeting a target of 7% to find a significant difference in complication rates at that threshold.

Although the prevalence of microalbuminuria has decreased previously, the prevalence of both borderline AER/ACR and microalbuminuria appears to have reached a plateau in the last three time periods. Although microalbuminuria remains uncommon in this age-group, it is of concern that almost one-third of adolescents had borderline elevation of AER/ACR, especially since we and others have shown previously this is risk factor for future development of microalbuminuria (22). Borderline AER/ACR was associated with recognized risk factors including DBP, older age, higher HbA_{1c}, higher weight SDS, higher insulin doses per kilograms (both surrogate markers for insulin resistance), male sex, and management with 1 to 2 injections per day (6,22,23). Notably, socioeconomic disadvantage was also significant in multivariate analysis. This may be a confounder for CSII/MDI use since in our population CSII is predominantly used by patients who have private health insurance, who are from higher socioeconomic groups (24).

The initial increase in peripheral nerve abnormalities over time also reached a plateau in the two recent time periods. We have shown previously a positive association between height and peripheral nerve abnormalities. In the current analysis, when peripheral nerve function was adjusted for height, surprisingly only

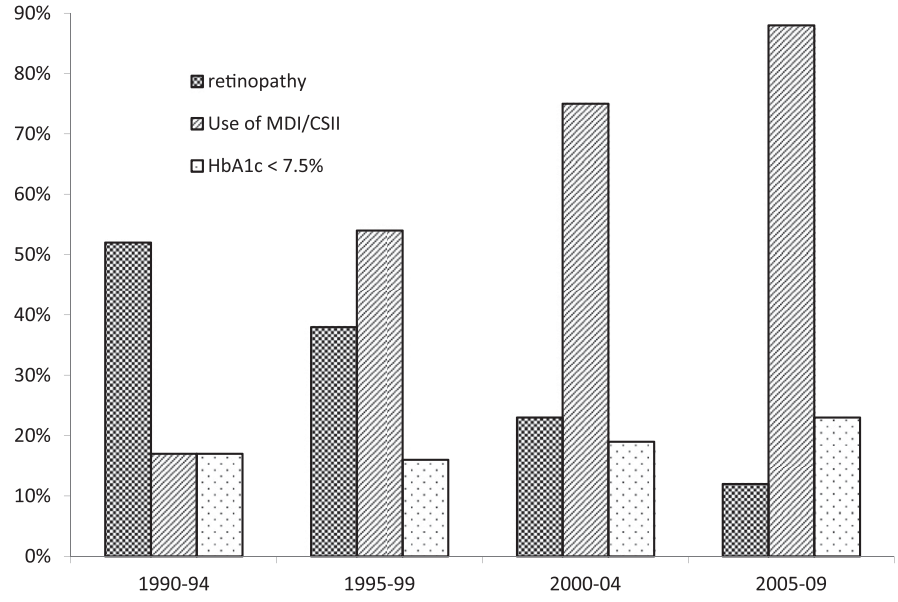

Figure 1—*Declining retinopathy in parallel with greater use of MDI/CSII and improving glycemic control in 1,604 adolescents with type 1 diabetes.*

fewer injections actually reduced the risk of peripheral nerve abnormalities without the more usual variables increasing the risk (7,25).

Both retinopathy and borderline AER/ACR were associated with an improvement in socioeconomic status over time. It is possible that there has been a bias toward higher socioeconomic status individuals who attended a complications assessment in recent years, in parallel with improved knowledge. The coding of socioeconomic status is postcode based and determined every 4 years by the Australian Bureau of Statistics; therefore the change in socioeconomic status may represent reclassification of the same area rather than a change in patient circumstances.

In conclusion, we have observed a marked decline in retinopathy in adolescents in the past 20 years in association with a decrease in HbA_{1c} and intensification of treatment regimens. Other microvascular complications have plateaued, with microalbuminuria remaining uncommon. We found some evidence for a specific benefit of CSII; ongoing observation of patients treated in this technological era will demonstrate whether CSII and other tools (such as continuous glucose monitoring) have specific advantages over MDI.

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E.D. contributed to statistical analysis and data interpretation and drafted the manuscript. M.E.C. contributed to data collection, statistical analysis, and data interpretation and wrote and revised the manuscript. S.H. contributed to data collection including retinal photography assessment. J.C. and A.K.F.C. contributed to data collection. K.C.D. contributed to data collection, statistical analysis, and data interpretation; wrote and revised the manuscript; and is the guarantor of this article.

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