Thirty-Year Time Trends in Diabetic Retinopathy and Macular Edema in Youth With Type 1 Diabetes

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OBJECTIVE

To examine trends in diabetic retinopathy (DR) and diabetic macular edema (DME) in adolescents with type 1 diabetes between 1990 and 2019.

RESEARCH DESIGN AND METHODS

We analyzed 5,487 complication assessments for 2,404 adolescents (52.7% female, aged 12–20 years, diabetes duration >5 years), stratified by three decades (1990–1999, 2000–2009, 2010–2019). DR and DME were graded according to the modified Airlie House classification from seven-field stereoscopic fundal photography.

RESULTS

Over three decades, the prevalence of DR was 40, 21, and 20% ($P < 0.001$) and DME 1.4, 0.5, and 0.9% ($P = 0.13$), respectively, for 1990–1999, 2000–2009, and 2010–2019. Continuous subcutaneous insulin infusion (CSII) use increased (0, 12, and 55%; $P < 0.001$); mean HbA_{1c} was bimodal (8.7, 8.5, and 8.7%; $P < 0.001$), and the proportion of adolescents meeting target HbA_{1c} <7% did not change significantly (8.3, 7.7, and 7.1%; $P = 0.63$). In multivariable generalized estimating equation analysis, DR was associated with 1–2 daily injections (odds ratio 1.88, 95% CI 1.42–2.48) and multiple injections in comparison with CSII (1.38, 1.09–1.74); older age (1.11, 1.07–1.15), higher HbA1c (1.19, 1.05–1.15), longer diabetes duration (1.15, 1.12–1.18), overweight/obesity (1.27, 1.08–1.49) and higher diastolic blood pressure SDS (1.11, 1.01–1.21). DME was associated with 1–2 daily injections (3.26, 1.72–6.19), longer diabetes duration (1.26, 1.12–1.41), higher diastolic blood pressure SDS (1.66, 1.22–2.27), higher HbA_{1c} (1.28, 1.03–1.59), and elevated cholesterol (3.78, 1.84–7.76).

CONCLUSIONS

One in five adolescents with type 1 diabetes had DR in the last decade. These findings support contemporary guidelines for lower glycemic targets, increasing CSII use, and targeting modifiable risk factors including blood pressure, cholesterol, and overweight/obesity.

Adolescents with type 1 diabetes are at risk for developing diabetic retinopathy (DR) and diabetic macular edema (DME), which may ultimately progress to blindness in adulthood (1,2). The prevalence of DR in young people with diabetes from

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Australia, France, U.K., and the U.S. ranges from 3.4 to 20.1% (2001–2020) (3–8). This was as high as 41% (9) in Australia prior to the publication of the Diabetes Control and Complications Trial (DCCT) in 1993 (10). To date, there are no comparative data on DME in young adolescents with type 1 diabetes. The age-standardized prevalence of DME per 100 adults with type 1 diabetes is 14.3% (95% CI 13.86–14.64) (11), with up to 29% of adults developing DME over 25 years of follow up (12). We previously reported, parallel to the increased use of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) therapy, a declining prevalence of DR in Australian adolescents with type 1 diabetes from 53 to 12% between 1990 to 2009 (13) and an associated reduction in DR in adolescents using CSII compared with MDI between 2000 and 2014 (7).

The International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines recommend initial dilated fundus examination 2–5 years after diabetes diagnosis once individuals reach 11 years of age or at the time of puberty, unless additional considerations necessitate earlier assessment (14). In a targeted review of the DCCT, no cases of severe nonproliferative DR (NPDR) were reported in patients under the age of 18 years; the review therefore suggested that a single assessment may be cost-effective and safe in adolescents (15). Nevertheless, proliferative DR (PDR) has been detected in children as young as 6 years of age (6). As such, understanding the contemporary prevalence and severity of DR in the adolescent population is important to inform screening guidelines.

In this study of trends in DR prevalence over 30 years among adolescents with type 1 diabetes we hypothesized that the prevalence of DR and DME would decrease over time and be lower in those using CSII. We also hypothesized that glycemic control would similarly improve across the three decades.

RESEARCH DESIGN AND METHODS

Study Design and Population

This prospective cohort study included 2,404 adolescents with type 1 diabetes assessed at the Diabetes Complications Assessment Service at The Children's Hospital at Westmead (CHW) from 1990 to 2019. The referral base is primarily from CHW, a tertiary diabetes center with a large catchment area in Greater Western Sydney, in addition to external referrals from elsewhere in New South Wales. Only 1.5% of study participants resided in the local hospital postcode, demonstrating a wide catchment area. Participants were recruited prospectively for an observational study of complications trends. Eligibility criteria were age 12–20 years, diagnosis of type 1 diabetes (according to the ISPAD Clinical Practice Consensus Guidelines definition [16], with diabetes autoantibody testing standard practice), and disease duration of at least 5 years. Informed consent was obtained from participants, or their guardians on behalf of minors, enrolled in the study. The study was approved by the CHW ethics committee in adherence to the Declaration of Helsinki (Human Research Ethics Committee no. 2020/ETH00326).

Complications Assessment

Assessment was undertaken during a 2-h clinic visit by the Diabetes Complications Assessment Service as previously described (7,13). DR was detected with stereoscopic fundal photography of seven fields. Retinal images were graded from slides between 1990 and 2004 and from the IMAGEnet R4 system thereafter (with the TOPCON 50X Retinal Camera for both slides and digital images). Grading masked to clinical data was performed by a consultant ophthalmologist (1990–2005, S.H.) and an orthoptist (2006–2019, A.P.) and adjudicated by consultant ophthalmologists (2006–2014, S.H., and 2014–2019, G.L.). Images were graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification (13,17). Grade 21 was classified as mild NPDR and defined as one or more microaneurysms, grades 31–41 as moderate NPDR, grade 51 as severe NPDR, and grade 61 as PDR as per the international clinical severity scales for DR and DME (18). Intragrader concordance after repeated assessment (n = 100 eyes) produced a weighted κ = 0.86 (95% CI 0.72–0.99). Intergrader reliability measurement with independent reassessment by two graders (n = 100 eyes) produced a weighted κ = 0.81 (95% CI 0.70–0.91). These κ values indicate excellent agreement. The retinopathy grade of the worst eye was used in analyses for this study. The prevalence of DR was determined at the last visit for each individual during each time period. DME was defined from stereoscopic retinal photographs according to ETDRS criteria (19). Optical coherence tomography data were not available.

Glycemic control was assessed by glycosylated hemoglobin (GHb) colorimetrically before February 1994 (20). From 1994 to 2009, HbA_{1c} measurement was assessed with high-quality liquid chromatography with the VARIANT analyzer (Bio-Rad Laboratories, Hercules, CA) and subsequently the ADAMS (ARKRAY, Kyoto, Japan) from January 2010 onward; ADAMS = 1.0566 × VARIANT, R^2 = 0.98). GHb values were converted to HbA_{1c} (21) (Diamat = 1.9088 + 0.0043 × GHb; R^2 = 0.85). HbA_{1c} was recorded as an NGSP percentage and converted to mmol/mol with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardization formula ([10.93 * NGSP HbA_{1c}] − 23.50) (22). The normal range for HbA_{1c} is 4–6%.

Cholesterol was measured with a Beckman CX5 (1990–1999), a Dimension RxL (2000– 2005), and a VITROS analyzer (Ortho Clinical Diagnostics) from 2005 onward. Elevated total cholesterol was defined as ≥5.5 mmol/L. Height (to the nearest 0.1 cm) was measured with a Harpenden Stadiometer and weight (to the nearest 0.1 kg) with electronic scales at each clinic visit. BMI was calculated as weight in kilograms divided by the square of height in meters. These measurements were converted to BMI SDS with use of the 2000 Centers for Disease Control and Prevention reference standards (23). Overweight was classified as a BMI ≥85th and <95th percentile (BMI SDS ≥1.036 and <1.645), and obesity was classified as BMI ≥95th percentile (BMI SDS ≥1.645). Systolic (SBP) and diastolic (DBP) blood pressure were measured after 5 min rest in the seated position, by auscultation using an appropriate sized cuff, with age- and sex-related SDS calculated according to the methodology of the U.S. Task Force Report (24). Socioeconomic status (SES) was classified into deciles with a postcode-based system according to the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) database (25). The 2016 Index of Relative Socio-economic Advantage and Disadvantage was used to separate individuals into two SES groups, SES disadvantaged (lower three deciles)

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Table 1—Patient demographics and retinal complications in adolescents with type 1 diabetes stratified by time period (10-year intervals)

	T1 (1990–1999)	T2 (2000–2009)	T3 (2010–2019)	*P*
n	771	1,080	910	—
Female sex	413 (54)	590 (55)	453 (50)	0.08
Age (years)	16.5 [15.0–18.1]	16.9 [15.3–18.1]	17.0 [15.5–18.1]	<0.01
Duration (years)	8.7 [6.4–11.7]	8.9 [7.0–11.8]	9.4 [7.3–12.3]	<0.001
HbA_{1c}, %	8.7 [7.8–9.8]	8.5 [7.7–9.5]	8.7 [7.9–9.9]	<0.001
HbA_{1c}, mmol/mol	72 [62–84]	69 [61–80]	72 [63–85]	<0.001
HbA_{1c} <7%	63 of 755 (8.3)	83 of 1,072 (7.7)	63 of 891 (7.1)	0.63
Insulin therapy				<0.001
One to two injections	422 of 755 (56)	197 of 1,047 (19)	28 of 888 (3)	
MDI	333 of 755 (44)	720 of 1,047 (69)	369 of 888 (42)	
CSII	0 of 755 (0)	130 of 1,047 (12)	491 of 888 (55)	
Insulin dose (units/kg/day)	1.1 [0.91–1.30]	1.1 [0.90–1.31]	0.91 [0.77–1.13]	<0.001
Height SDS	0.09 [−0.53 to 0.72]	0.20 [−0.46 to 0.89]	0.15 [−0.53 to 0.81]	0.02
Weight SDS	0.68 [0.10–1.13]	0.84 [0.30–1.35]	0.76 [0.16–1.33]	<0.001
BMI SDS	0.64 [0.15–1.10]	0.81 [0.27–1.27]	0.73 [0.09–1.31]	<0.001
Overweight*	171 of 751 (22.8)	282 of 1,068 (26.4)	219 of 892 (24.55)	0.21
Obese†	40 of 751 (5.3)	112 of 1,068 (10.5)	104 of 892 (11.7)	<0.001
SBP SDS	0.49 [0–0.97]	0.00 [−0.81 to 0.59]	0.03 [−0.61 to 0.64]	<0.001
DBP SDS	0.71 [0.25–1.2]	0.39 [−0.18 to 0.96]	−0.07 [−0.51 to 0.54]	<0.001
Cholesterol (mmol/L)	4.4 [3.8–5.1]	4.4 [3.8–5.0]	4.4 [3.8–5.0]	0.79
Cholesterol >5.5 mmol/L	108 of 736 (14.7)	132 of 1,031 (12.8)	106 of 862 (12.3)	0.34
SES disadvantaged	143 of 755 (18.9)	195 of 1,079 (18.1)	207 of 909 (22.8)	0.03
Ethnic minority	19 of 206 (9.2)	107 of 804 (13.3)	218 of 564 (27.9)	<0.01
Retinal complications				
DR	296 of 734 (40.3)	226 of 1,060 (21.3)	177 of 887 (20.0)	<0.001
DR grades				<0.001
Mild NPDR (grade 21)	201 (27.4)	181 (17.1)	144 (16.2)	
Moderate NPDR (grade 31)	91 (12.4)	45 (4.25)	26 (2.93)	
Moderate NPDR (grade 41)	4 (0.5)	0 (0)	3 (0.3)	
Severe NPDR (grade 51)	0 (0)	0 (0)	2 (0.2)	
PDR (grade 61)	0 (0)	0 (0)	2 (0.2)	
DME	10 (1.4)	5 (0.5)	8 (0.9)	0.13

Data are *n* (%), median [interquartile range]. *Overweight BMI SDS >1.036 and <1.645; †Obese BMI SDS ≥1.645.

and SES advantaged (upper seven deciles), as previously described (13). Ethnicity was classified as minority versus nonminority from 27 subcategories within the Australasian Diabetes Data Network (ADDN) database as previously described (26). The number of injections per day, use of MDI/CSII, and total insulin dose per kilogram per day were recorded. Total insulin dose per kilogram per day was used as a proxy for insulin sensitivity in the absence of key variables required to calculate the insulin sensitivity score validated in the SEARCH for Diabetes in Youth (SEARCH) study.

Statistical Analysis

All statistical analyses were conducted with Stata 15.1 (27). Summary statistics are reported as mean ± SD for normally distributed data or median and interquartile range for skewed data. Individuals were stratified according to time periods 1990–1999 (T1), 2000–2009 (T2), and 2010–2019 (T3). For individuals seen more than once during a given time period, only their last visit in each time period was included in the demographic analysis (Table 1). Continuous parametric data were compared across the three time periods using ANOVA for normally distributed variables and the Kruskal-Wallis test for skewed data. χ^2 tests were used to compare categorical data across groups.

Generalized Estimating Equations (GEE) were used to examine factors associated with DR and DME, with all visits in each decade included in the models. Explanatory variables included in the models were sex, age, duration of diabetes, visit HbA_{1c}, height SDS, weight SDS, BMI SDS, overweight/obesity (BMI ≥85th percentile), elevated cholesterol (>5.5 mmol/L), SBP SDS, DBP SDS, insulin therapy (one to two injections per day vs. MDI vs. CSII),

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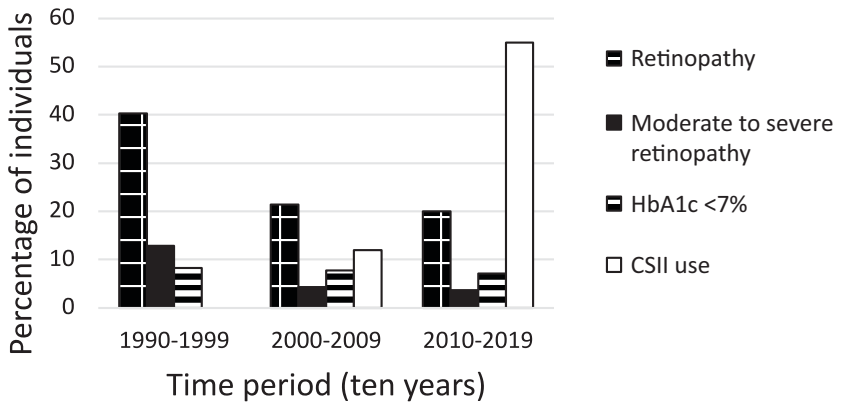

Figure 1—Retinopathy, glycemic control, and pump therapy in adolescents with type 1 diabetes: stabilizing of DR and glycemic control despite greater use of CSII in 2,404 adolescents with type 1 diabetes.

insulin dose per kilogram body weight per day (recategorized as <1.3 or >1.3 units/kg/day), ethnicity (minority or nonminority), and SES (SEIFA [comparing lower three deciles and upper seven deciles]). The current ISPAD target of 7% for adolescents with diabetes was used to define target HbA_{1c} as a categorical variable (28). Cholesterol did not meet normality assumptions for inclusion as a continuous variable, and BMI SDS did not reach significance in univariable analysis. Thus, categorical variables were included to test for these modifiable risk factors, namely, elevated cholesterol (>5.5 mmol/L) and overweight/obesity categories.

A stepwise process of backward elimination was used to construct the multivariable models using significant variables ($P < 0.25$) and potential confounders from the preceding univariable models. The multivariable model for DR included three variables for insulin therapy (one to two injections per day vs. MDI vs. CSII), time period (T1, T2, and T3), and explanatory variables with $P < 0.25$ in univariable analysis. The two models for DME included only two variables for insulin therapy (one to two injections per day vs. MDI/CSII) and a maximum of three explanatory variables with $P < 0.25$ in univariable analysis to ensure sufficient statistical power due to the small number of DME cases. Interaction terms between time period and insulin therapy, SES and insulin therapy, and HbA_{1c} and insulin therapy were examined in all models.

RESULTS

Data for 2,404 eligible individuals (52.7% female) were included in the study, with results from 5,487 complication assessments included in the analysis (median visit per participant 2, range 1–9). As such, some individuals were assessed in more than one time period. At the last visit the median age of all participants was 16.9 years (IQR 15.35–18.12) and the median duration of diabetes was 8.9 years (IQR 6.88–11.75). Participant characteristics and prevalence of DR at the last visit per decade, stratified by time period, are shown in Table 1.

Despite a relatively stable HbA_{1c}, the prevalence of DR decreased from 40% in T1 to 21% in T2, stabilizing in T3 (20%) (Fig. 1). The median age and duration of diabetes increased across the time periods. Glycemic control varied over time, with median HbA_{1c} declining to a nadir of 8.5% (69 mmol/mol) in T2 and subsequently increasing to 8.7% (72 mmol/mol) in T3. During T2, the proportion of individuals with HbA_{1c} >9% (>75 mmol/mol) was significantly lower than in the two neighboring time periods (T1 47%, T2 39%, T3 45%; $P = 0.002$). There was no significant change in the proportion of individuals meeting the target of HbA_{1c} <7% (<53 mmol/mol; $P = 0.6$, Fig. 1), while the proportion of individuals using CSII increased significantly over time (Fig. 1). Median HbA_{1c} was not significantly different between those receiving one to two injections daily, MDI, and CSII (8.7% [72 mmol/mol], 8.7% [72 mmol/mol], and 8.6% [71 mmol/mol], respectively; $P = 0.6$). The proportion of overweight individuals remained stable, yet the prevalence of obesity increased (5.3, 10.5, 11.7%; $P < 0.001$). There was a significant increase in the proportion of SES disadvantaged individuals and adolescents of an ethnic minority over the three time periods. SBP SDS did not reach significance in the univariable DME or multivariable DR model.

The prevalence and severity of DR increased with age and duration of disease. Importantly, 12.8% of individuals aged 12 to <14 years, 24.1% aged 14 to <16 years , 26.2% aged 16 to <18 years , and 34.5% aged 18 to 20 years had detectable DR after 5 years of type 1 diabetes, 14–28% of whom had moderate NPDR or PDR. In the last decade, one in five adolescents with type 1 diabetes had DR.

Among individuals with diabetes duration >10 years, 36.4% had detectable DR (compared with 19.8% with duration <10 years), 27.5% and 0.5% of whom had moderate and severe NPDR, respectively (Supplementary Materials). Only individuals with disease duration >10 years had severe NPDR or PDR. These four individuals (50% male) with severe NPDR or PDR had a longer duration of diabetes (mean ± SD 13.4 ± 1.78 years; $P = 0.02$), younger age of diagnosis (2.76 ± 0.99 years; $P < 0.01$), lower weight SDS (–0.4 ± 2.14; $P = 0.01$), and higher cholesterol (5.4 ± 1.44 mmol/L; $P = 0.05$) than the general study population (Supplementary Materials). For two adolescents with preceding DR grading visits, progression occurred over a 2.2-year duration from mild to severe NPDR and from no DR to PDR, respectively.

There was no significant time trend in DME, with a low prevalence across all three time periods (1.4, 0.5, 0.9%; $P = 0.13$). DME was present in 43 complication assessments of 34 individuals. DR was concurrently observed in 40 of these assessments (93%). Of these 34 young people, DME was identified in 20 during T1 (1990–1999), 6 in T2 (2000–2009), and 8 in T3 (2010–2019). Those with DME had a longer duration of diabetes (mean ± SD 10.5 ± 3.4 years; $P < 0.01$) and higher HbA_{1c} (9.5 ± 1.6%, 80 ± 17.1 mmol/mol; $P < 0.01$) than those without DME. Of the 34 individuals (76%), 25 resided in areas of SES disadvantage, compared with 21% of those without DME ($P < 0.001$).

Multivariable Analysis

Factors associated with increased risk of DR in GEE included one to two injections

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Table 2—GEE for factors associated with retinal complications in adolescents with type 1 diabetes

Complication and variable	Univariable Model		Multivariable Model	
	OR (95% CI)	*P*	OR (95% CI)	*P*
DR				
Insulin treatment*				
One to two injections	2.39 (1.92–2.97)	<0.001	1.88 (1.42–2.48)	<0.001
MDI	1.61 (1.32–1.97)	<0.001	1.38 (1.09–1.74)	<0.01
Time period†				
1990–1999	2.15 (1.77–2.61)	<0.001	2.07 (1.61–2.66)	<0.001
2000–2009	1.08 (0.90–1.31)	0.414	0.96 (0.78–1.20)	0.74
Overweight/obese (BMI SDS >1.036)	1.17 (1.01–1.36)	0.043	1.27 (1.08–1.49)	<0.005
Duration of diabetes (years)	1.16 (1.13–1.19)	<0.001	1.15 (1.12–1.18)	<0.001
Age (years)	1.17 (1.13–1.21)	<0.001	1.11 (1.07–1.15)	<0.001
DBP SDS	1.25 (1.16–1.35)	<0.001	1.11 (1.01–1.21)	0.02
HbA_{1c} %	1.10 (1.05–1.15)	<0.001	1.10 (1.05–1.15)	<0.001
DME (model 1)				
One to two injections‡	3.39 (1.76–6.52)	<0.001	3.26 (1.72–6.19)	<0.001
DBP SDS	1.68 (1.24–2.28)	0.001	1.66 (1.22–2.27)	<0.01
HbA_{1c} %	1.28 (1.07–1.54)	0.006	1.28 (1.03–1.59)	0.03
Duration of diabetes (years)	1.23 (1.12–1.35)	<0.001	1.26 (1.12–1.41)	<0.001
DME (model 2)				
One to two injections‡	3.39 (1.76–6.52)	<0.001	3.32 (1.76–6.26)	<0.001
Elevated cholesterol (>5.5 mmol/L)	4.17 (2.00–8.67)	<0.001	3.78 (1.84–7.76)	<0.001
DBP SDS	1.68 (1.24–2.28)	0.001	1.53 (1.12–2.10)	<0.01
Duration of diabetes (years)	1.23 (1.12–1.35)	<0.001	1.25 (1.11–1.40)	<0.001

OR, odds ratio. *CSII used as referent group; †Time period 2010–2019 used as referent group; ‡MDI/CSII used as referent group.

per day or MDI versus CSII, decade T1 versus T2, increasing age, higher HbA_{1c}, longer duration of diabetes, overweight/obesity, and higher DBP SDS (Table 2). SES and ethnicity were not significant. The odds of DR were higher for those treated with one to two injections daily (1.88, 95% CI 1.42–2.48) and MDI (1.38, 95% CI 1.09–1.74) versus CSII ($P < 0.01$). The odds of DR were higher for T1 (2.07, 95% CI 1.61–2.66) than the most recent decade ($P < 0.001$) but not different for T2 versus T3. Being overweight or obese increased the risk of DR by 30%.

Higher HbA_{1c} as a continuous variable was consistently associated with DR in multivariable analysis (Table 2). This association remained significant when HbA_{1c} was incorporated as a categorical threshold of >7% (odds ratio [OR] 1.32, 1.02–1.72, $P = 0.03$).

Factors associated with DME included one to two injections per day versus MDI/CSII, longer duration of diabetes, higher DBP SDS, and higher HbA_{1c} (model 1) and elevated cholesterol (model 2) (Table 2). Interaction terms in the final GEE models for DR and DME were not significant.

CONCLUSIONS

In this 30-year prospective study of 2,404 adolescents with type 1 diabetes, we found that the prevalence of DR decreased by 47.5% over the first two decades (40 to 21%) and stabilized over the last 10 years (21 to 20%). The overall prevalence of DME was 0.5–1.4%. While this was an observational nonrandomized cohort, we confirm our previously observed association between more intensive management with MDI/CSII and reduced DR prevalence (7,13). We further confirm that CSII use was associated with a 38% lower prevalence of DR compared with MDI use. This finding was independent of other important risk factors, namely HbA_{1c}, duration, time period, age, overweight/obesity, and DBP.

Disappointingly, in those with >5 years' diabetes duration undergoing DR screening at our referral clinic, the median HbA_{1c} and proportion of individuals meeting the current ISPAD target of HbA_{1c} <7% remained relatively unchanged. In the last decade, after 5 years of type 1 diabetes, early DR was detected in one in five adolescents aged >12 years, of whom a further quarter had moderate NPDR—not all of which, the literature suggest, will progress to severe NPDR or PDR (10,14).

The prevalence of DR in the last time period (2010–2019) was 20%, which is within the 3.4–20.1% range reported in studies of adolescents with type 1 diabetes (2001–2020) (3–6,8). Direct comparison with these earlier studies is difficult due to differences in age, DR assessment method, duration of follow-up, and treatment modalities. Nevertheless, the high prevalence of DR in the last decade of this study possibly indicates the increasing diabetes duration, age, and obesity prevalence over the last three decades. As such, this cohort may indicate a more at-risk demographic reflective of the study's inclusion criteria (12–20 years of age and >5 years' diabetes duration) and our role as a tertiary referral center in Western Sydney. Importantly, DR was significantly associated with HbA_{1c} such that a 1% increase in HbA_{1c} was associated with a 10% increased prevalence of DR before and after adjustment for covariates. Furthermore, the proportion of individuals meeting the HbA_{1c} target of 7% (28) was low and there was a 32% increased prevalence of DR among those with an HbA_{1c} above this target

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in multivariable analysis. This supports ISPAD's HbA_{1c} target of 7% in the absence of contraindications or adverse events (28).

We previously reported the risk factors identified in this study (13) but now additionally include overweight/obesity, substitute SBP for DBP, and provide more granular analysis of insulin therapy. CSII use increased from 0% in T1 to 55% in T3 (Fig. 1). In keeping with previous reports (7,8,29,30), CSII use was associated with reduced prevalence of DR independent of HbA_{1c}. This may represent more physiological insulin administration. Alternatively, acknowledging the absence of continuous glucose monitoring data, this trend could suggest that CSII may confer a risk benefit unrelated to its modest influence on HbA_{1c} and may mitigate DR risk by reducing glycemic variability and improving time in range independent of HbA_{1c} levels (29–31).

DME is a critical cause of visual impairment in individuals with diabetes and can occur in 12.3–40.0% of adults with type 1 diabetes (2,12,32). This is the first study to report DME in a large cohort of adolescents with type 1 diabetes. It was associated with non-MDI/CSII use, longer duration of diabetes, greater DBP, elevated cholesterol, and higher HbA_{1c}. These associations mirror those reported in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study (2) and other observational populations, in which the prevalence and cumulative incidence of DME was 12.9% (32), 8.3% (33), and 29% (12).

Importantly, several of the risk factors for DR and DME in our study are modifiable. Hypertension may precipitate structural changes in retinal vasculature contributing to DR and DME (12,34). Longitudinal studies have identified elevated DBP as a significant predictor of DR progression (35) and DME development (2) in adults with type 1 diabetes. We similarly report this association in adolescents. Inflammation is also implicated in the pathogenesis of DME, and elevated cholesterol levels are causally linked to low-grade inflammation (33,36). Moreover, the association between overweight/obesity and PDR reported in other observational studies (2,35) was likewise present in our cohort. The DCCT previously demonstrated a 76% and 46% reduction in the incidence of DR and DME, respectively, with the implementation of intensive glycemic control (1). In addition to intensive insulin therapy, non-glycemic-related interventions including blood pressure control, BMI reduction, and lipid-lowering lifestyle changes may reduce the risk of DR and DME. However, there is a lack of clinical trial evidence that pharmacological blood pressure control limits the progression of DR and DME in individuals with type 1 diabetes (37). Prospective clinical trials are therefore required to examine whether improvements in these modifiable risk factors will produce a significant reduction in DR and DME independent of tight glycemic control.

The strengths of this study include the large sample size of 2,404 adolescents, with 5,487 complication assessments collected prospectively across 30 years. All individuals were assessed at a single center, and comprehensive data were collected at each clinic visit. There were few changes to the complication assessment methods throughout the 30-year study period, and there was only a small number of changes in program personnel. The large sample size and rich data set permitted examination of multiple variables and GEE analysis with inclusion of interaction terms.

There are several considerations that may affect the generalizability of our results. In two retrospective reviews, of a British diabetes eye screening program (n = 2,125) (5) and an American tertiary referral ophthalmology center (n = 293) (4), investigators reported DR prevalence of 8–20% and 3.4%, respectively. Our cohort was also from a tertiary referral center and as such could be biased toward more rigorous monitoring, better glycemic control, and underrepresentation of DR. However, the individuals included in this study had a longer duration of diabetes and greater prevalence of DR than reported among several published populations (3,4,8), potentially suggesting a more at-risk population. The study findings are representative of the largest cohort of adolescents with type 1 diabetes followed at a single New South Wales tertiary center. While this may limit generalizability, the prevalence of DR is comparable with that in other published international cohorts (6), and as such our recommendations are pertinent to the global type 1 diabetes community.

Given the reduced prevalence of DR for individuals in 2000–2019 compared with 1990–1999 (after adjustment for insulin therapy type), we cannot exclude a cohort effect because younger individuals may have a better prognosis secondary to advances in diabetes management in the last 30 years. This study only included adolescents visiting the Diabetes Complications Assessment Service, and those achieving target HbA_{1c} may have been less likely to be referred to our service. Changes in follow-up for participants in our clinics may have also affected the results; however, attrition from this cohort over time was unable to be assessed.

Optical coherence tomography, the current gold standard for diagnosing DME, was not used in our study, as it only came into widespread clinical use in the last decade. As a result, some DME cases may not have been identified that would meet contemporary diagnostic criteria. Nonetheless, this should not influence our main conclusions, as we used the same diagnostic criteria (stereoscopic retinal photographs according to ETDRS definitions) throughout the entire study duration. The transition from slide to digital retinography in 2004 may have increased sensitivity to the early signs of NPDR. This reinforces that the reduction in the prevalence of DR in the second decade represents a true decrease in disease. The individual HbA_{1c} measurement available for each complication assessment may not accurately reflect the overall glycemic control of the adolescent.

The low incidence rate, mild severity, and paucity of treatable DR in adolescents have driven appeals to reevaluate screening guidelines (38). Investigators in a 2019 review of the DCCT data reported no cases of severe NPDR/PDR and one case of clinically significant macular edema in individuals $<$18 years of age and recommended that a single DR screening examination be considered as safe and more economically viable in a subgroup of adolescents (15). In juxtaposition with this 2019 review, our study identified 4 individuals with severe NPDR/PDR and 27 with DME $<$18 years of age, reaffirming that a burden of severe DR and DME does exist in young people. Compared with this adolescent DCCT cohort (15), our adolescents had a longer duration of diabetes and higher BMI, which may have contributed to the greater prevalence of clinically significant ocular compilations (2).

Progression to severe NPDR/PDR occurred over a 2.2-year period in two

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adolescents without interim study screening. Albeit small, this is important given the potential for early and rapidly progressive disease with debilitating consequences (6). This reinforces the importance of incorporating risk factors such as high BMI into screening decisions as recommended by ISPAD and perhaps underscores the need for an objective clinical risk stratification tool (14). Given the inverse relationship between age-specific diabetes education and diabetes-related complications, screening is advantageous in facilitating early identification of ocular complications and subsequent counseling despite the low prevalence of severe DR/DME requiring procedural intervention (39). Currently underway is a randomized control trial aiming to determine the acceptability and safety of annual versus risk-based screening in individuals aged >12 years with diabetes, which may provide the requisite data to support appropriate screening guideline adaptations (40). Artificial intelligence with nonmydriatic cameras may further reduce the cost and burden of such screening.

In conclusion, despite an early reduction in DR prevalence from the first to the second decade, there was minimal reduction over the third decade. One in five adolescents >12 years of age has early DR after 5 years of diabetes, while a further quarter of these individuals have moderate disease. In our cohort, both severe NPDR and PDR occurred prior to 18 years of age, albeit uncommonly. CSII is associated with a lower prevalence of DR, and we theorize that reduced glycemic variability in CSII users underpinned this risk reduction, given the largely unchanged HbA_{1c} levels across 30 years of follow up. HbA_{1c}, cholesterol, overweight/obesity, and DBP remain modifiable risk factors for DR and DME. Despite intensified therapy, HbA_{1c} has remained relatively level and well above suggested thresholds for adolescents with type 1 diabetes. Further prospective studies on CSII users with the addition of glycemic variability data will provide information to refine risk stratification, elucidate the impact of modifiable risk factor mitigation, and inform best practice and screening guidelines.

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