Long term risk of severe retinopathy in childhood-onset type 1 diabetes: a data linkage study

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Abstract

Objectives: To determine the relationship between glycaemic control trajectory and the long term risk of severe complications in people with type 1 diabetes mellitus, as well as the effects of paediatric and adult HbA1c levels.

Design, setting, participants: Data linkage study of data for adults with childhood-onset type 1 diabetes (diagnosed during 1975–2010) who had transitioned from paediatric diabetes care at the Royal Children’s Hospital (Melbourne) to adult diabetes care at the Royal Melbourne Hospital during 1992–2013.

Main outcome measures: Severe complications were categorised as severe diabetic retinopathy (SDR), chronic kidney disease, ulceration or amputation, and death. Mean HbA1c levels were calculated for the paediatric and adult periods. Four glycaemic control trajectories were defined according to mean paediatric and adult HbA1c levels: stable low (paediatric and adult HbA1c ≤ 66 mmol/mol); improving (paediatric HbA1c > 66 mmol/mol, adult HbA1c ≤ 66 mmol/mol); worsening (paediatric HbA1c ≤ 66 mmol/mol, adult HbA1c > 66 mmol/mol); and stable high (paediatric and adult HbA1c > 66 mmol/mol).

Results: 503 eligible participants (253 men) were identified, 26 (5.2%) of whom had at least one severe complication, including 16 with SDR (3.2%). No-one in the stable low group, but 4% of the improving, 1% of the worsening, and 7% of the stable high groups developed SDR. Higher mean paediatric (per 10.9 mmol/mol increase: odds ratio [OR], 2.9; 95% CI, 1.9–4.3; P < 0.01) or adult HbA1c levels (OR, 1.3; 95% CI, 1.2–1.5; P < 0.01) were associated with increased risk of SDR, as was longer duration of type 1 diabetes (per additional year: OR, 1.3; 95% CI, 1.2–1.5; P < 0.01).

Conclusion: SDR was associated with higher paediatric HbA1c levels, independent of glycaemic control during adulthood; it was not documented in patients with a stable low glycaemic control trajectory.

Methods

Study design

We undertook a retrospective cohort study of data collected from the time of diagnosis of type 1 diabetes in childhood until the time of our analysis (November 2013). Adults with a diagnosis of type 1 diabetes5 (diagnosed in childhood during 1975–2010) were included if they had attended at least one specialist adult diabetes clinic at the Royal Melbourne Hospital, and their care had been transferred from the paediatric diabetes clinic at the Royal Children’s Hospital (Melbourne) during 1992–2013. Individuals who had been lost to follow-up at the time of care transition from the paediatric diabetes clinic or who had died were therefore excluded. The choice of transition referral centre follows a discussion between the physician and young adult, and is not based on any biological or clinical criteria. Because of its proximity, the Royal Melbourne is the main adult referral centre for patients who transition from the Royal Children’s Hospital, receiving about 40% of its transitioning cohort.

We used a data linkage system, BioGrid Australia, that facilitates linkage of de-identified clinical data from member
Research

Main outcomes and measures

Severe complications. The primary outcome of interest was a database record of diabetes-specific microvascular complications; in this study, only the most severe forms were considered. The date and cause of death were obtained from the NDI. Severe diabetic retinopathy (SDR) included one or more of maculopathy, proliferative retinopathy, and a need for photocoagulation surgery. Chronic kidney disease (CKD) was defined by a glomerular filtration rate of less than 60 mL/min/1.73 m² (stage 3 CKD or worse), calculated from serial creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Ulceration and amputation were recorded according to the clinical database files.

Glycaemic control. HbA1c levels were summarised as paediatric (mean of all pre-transition paediatric clinic measurements), adult (mean of all post-transition measurements as an adult), and life course values (mean HbA1c level from diagnosis to November 2013). The glycaemic control trajectory was defined across the life course, with 66 mmol/mol set as the upper cut-off value for good glycaemic control. This value was preferred to the standard paediatric target of 58 mmol/mol because it was anticipated that some of the cohort had commenced treatment before publication of the DCCT findings upon which the current HbA1c target values are based. The median HbA1c level in children aged 0–18 years with type 1 diabetes in Australia in 2009 was reported to be 66 mmol/mol; this was also the median HbA1c level for a cohort of children who had recently transitioned from care at the Royal Children’s Hospital.

Each individual was assigned to one of four glycaemic control trajectory groups:

- stable low (mean paediatric and adult HbA1c ≤ 66 mmol/mol);
- improving (mean paediatric HbA1c > 66 mmol/mol, mean adult HbA1c ≤ 66 mmol/mol);
- worsening (mean paediatric HbA1c ≤ 66 mmol/mol, mean adult HbA1c > 66 mmol/mol); or
- stable high (paediatric and adult mean HbA1c > 66 mmol/mol).

Statistical analyses

Differences between the trajectory groups in participant characteristics, HbA1c levels, and complications were examined by one-way ANOVA (continuous variables) or in $\chi^2$ tests (categorical variables). The standardised mortality ratio was calculated as the ratio of the number of observed deaths to the number of expected deaths in the general population, based on 2012 Australian Bureau of Statistics data for Victoria. SDR was the only complication we examined in a regression analysis, as the aetiology of the other outcome measures could not be precisely defined. The relative effect of paediatric and adult glycaemic control on the risk of developing SDR was assessed by generalised estimating equation (GEE) analysis, which could allow for unmeasured variables and confounders. Statistical analyses were performed in Stata 13.0 (StataCorp); $P < 0.05$ was deemed statistically significant.

Ethics approval

The study received ethics approval from all participating institutions, the Royal Children’s Hospital Human Research Ethics Committee (reference, 31206), BioGrid (project reference, 201202/1), and the Australian Institute of Health and Welfare Research Ethics Committee (reference, EC2013-2-30).

Results

Participant characteristics

We identified 503 people (including 253 men) who were diagnosed with type 1 diabetes during 1975–2010 and had transitioned from paediatric to adult diabetes services over a 21-year period (1992–2013) at a mean age of 18.4 years (standard deviation [SD], 0.9 years; Box 1). The mean age at diagnosis was lower for girls (9.6 [SD, 3.9]) than boys (10.3 [SD, 4.1]) years ($P < 0.05$) but higher for women at the time of our analysis (28.8 [SD, 6.7] v 27.2 [SD, 5.7] years; $P < 0.05$). The mean duration of type 1 diabetes was therefore longer for women (19.3 [SD, 7.8] v 16.9 [SD, 7.1] years; $P < 0.01$). The total number of HbA1c measurements per individual was 22.0 (SD, 13.0), 10.0 (SD, 8.1) and 29.6 (SD, 15.9) during the paediatric, adult and life course periods respectively; the corresponding mean HbA1c levels were 68 mmol/mol (SD, 13.1), 70 mmol/mol (SD, 17.5), and 68 mmol/mol (SD, 12.0) (Box 1).

Severe complications

At least one severe complication was documented for 26 participants (5.2%), including 16 with SDR (3.2%; Box 1). No severe complications were recorded in the paediatric dataset. Based on age- and sex-matched data from 2012 Victorian state data, the overall standardised mortality ratio in this cohort was 1.9 (95% CI, 0.7–4.3) (men, 1.3 [95% CI, 0.2–4.1]; women, 2.7 [95% CI, 0.7–7.4]).

Lifetime glycaemic control trajectory and risk of complications

For the stable low group (143 participants, 28%), the mean paediatric, adult and overall HbA1c levels were 57 mmol/mol (SD, 6.6), 57 mmol/mol (SD, 6.6), and 58 mmol/mol (SD, 3.3) respectively (Box 1). Only one person in this group had a documented complication (a 29-year-old man who had had an amputation).

The glycaemic profiles for the stable low, improving (82 participants, 16%), worsening (96 participants, 19%) and stable high trajectories (182 participants, 36%) are shown in Box 2. Given the low frequency of complications, further analyses were restricted to SDR, for which a causative role for hyperglycaemia could be confidently assumed. No-one in the stable low group had developed SDR, but three in the improving (4%), one in the worsening (1%), and 12 in the stable high groups (7%) had developed SDR ($P = 0.004$; Box 1). The overall mean age of onset of SDR was 28.8 years (SD, 4.4) years (for the improving group, 23.9 years [SD, 3.7]; worsening group, 28.5 years; stable high, 30.3 years [SD, 3.9]; $P = 0.6$). However, the mean interval between diagnosis with type 1 diabetes and onset of SDR was shorter for the worsening (30.5 years) and stable high groups (28.1 years; SD, 0.8) than for the improving group (31.9 years; SD, 6.2; $P = 0.01$).

Paediatric HbA1c level and SDR risk in adulthood

GEE analysis that included significant variables from exploratory multivariate logistic regression models (online Appendix)
indicated that each 10.9 mmol/mol increase in paediatric HbA1c level was associated with an almost threefold risk of SDR (odds ratio [OR], 2.9; 95% CI, 1.9–4.3; *P* < 0.01); each 10.9 mmol/mol increase in adult HbA1c level was associated with a twofold risk (OR, 2.1; 95% CI, 1.4–3.1; *P* < 0.01). Longer duration of type 1 diabetes was also associated with an increased risk of SDR (per additional year: OR, 1.3; 95% CI, 1.2–1.5; *P* < 0.01).

**Discussion**

By incorporating all recorded HbA1c data from diagnosis onwards, this study offers a unique insight into a cohort of adults with childhood-onset type 1 diabetes who were not managed in clinical trials. None of those who maintained a mean HbA1c level of 66 mmol/mol or less from the time of diagnosis (the stable low group) developed SDR. The mean paediatric, adult and overall HbA1c levels in this group were each 58 mmol/mol or less, supporting the adoption of this target in paediatric practice.11 Each additional year of diabetes conferred a significant increase in the risk of SDR, and our data indicate that both paediatric and adult mean HbA1c levels are modifiable factors that moderate this risk. This is important for paediatric care providers, as 64.6% of participants remained in the same HbA1c level category (low or high) during the paediatric and adult periods, indicating that glycaemic control generally neither markedly deteriorates nor improves after the transition to adult services. This challenges the widely held belief that glycaemic control in young adults with type 1 diabetes improves during their mid- to late 20s following deterioration during the adolescent years,14 a premise that may not apply to every patient.

The major limitations of this study are its retrospective design and the low numbers of severe complications reported. Detailed

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### 1 Participant characteristics, HbA1c levels, and complication rates for all participants and for each glycaemic control trajectory group

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>Stable low</th>
<th>Improving</th>
<th>Worsening</th>
<th>Stable high</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% of participants)</td>
<td>503</td>
<td>143 (28%)</td>
<td>82 (16%)</td>
<td>96 (19%)</td>
<td>182 (36%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex (women)</td>
<td>250</td>
<td>58 (40%)</td>
<td>46 (35%)</td>
<td>44 (46%)</td>
<td>102 (56%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Age at diagnosis (years), mean (SD)</td>
<td>9.9 (3.9)</td>
<td>10.7 (4.1)</td>
<td>9.1 (3.9)</td>
<td>10.3 (4.2)</td>
<td>9.5 (3.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Duration of paediatric observation (years), mean (SD)</td>
<td>8.5 (4.2)</td>
<td>7.8 (4.1)</td>
<td>9.2 (4.1)</td>
<td>8.1 (4.6)</td>
<td>8.9 (4.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Range (years)</td>
<td>0.6–19.1</td>
<td>1.0–19.1</td>
<td>3.8–19.1</td>
<td>1.1–18.3</td>
<td>0.6–18.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Age at transition (years), mean (SD)</td>
<td>18.4 (0.9)</td>
<td>18.5 (0.8)</td>
<td>18.3 (0.8)</td>
<td>18.4 (1.1)</td>
<td>18.4 (1.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Duration of adult observation (years), mean (SD)</td>
<td>8.0 (5.8)</td>
<td>7.8 (5.3)</td>
<td>10.0 (6.9)</td>
<td>9.4 (5.5)</td>
<td>9.2 (5.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Range (years)</td>
<td>0.3–21.8</td>
<td>0.8–20.9</td>
<td>0.4–21.8</td>
<td>0.3–20.9</td>
<td>0.5–21.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Age at last follow-up (years), mean (SD)</td>
<td>27.9 (6.3)</td>
<td>26.4 (5.1)</td>
<td>30.4 (7.7)</td>
<td>27.6 (5.5)</td>
<td>28.4 (6.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of type 1 diabetes, (years), mean (SD)</td>
<td>18.1 (7.5)</td>
<td>15.5 (6.7)</td>
<td>21.3 (8.6)</td>
<td>17.5 (7.4)</td>
<td>18.9 (7.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>HbA1c measurements, mean number (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric</td>
<td>22.0 (13.0)</td>
<td>21.9 (12.8)</td>
<td>21.9 (15.5)</td>
<td>19.9 (12.8)</td>
<td>22.3 (12.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>Adult</td>
<td>10.0 (8.1)</td>
<td>11.3 (8.9)</td>
<td>11.1 (9.5)</td>
<td>9.5 (8.0)</td>
<td>8.6 (8.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>Lifetime</td>
<td>29.6 (15.9)</td>
<td>33.3 (15.4)</td>
<td>28.5 (18.0)</td>
<td>27.9 (14.3)</td>
<td>28.1 (15.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>HbA1c level (mmol/mol), mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric</td>
<td>68 (13.1)</td>
<td>57 (6.6)</td>
<td>74 (9.8)</td>
<td>60 (5.5)</td>
<td>78 (9.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adult</td>
<td>70 (17.5)</td>
<td>57 (6.6)</td>
<td>60 (5.5)</td>
<td>77 (10.9)</td>
<td>85 (17.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lifetime</td>
<td>68 (12.0)</td>
<td>58 (3.3)</td>
<td>67 (8.7)</td>
<td>65 (6.6)</td>
<td>79 (9.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Severe complications</td>
<td>26 (5.2%)</td>
<td>1 (1%)</td>
<td>6 (7%)</td>
<td>3 (3%)</td>
<td>16 (9%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Severe retinopathy</td>
<td>16 (3.2%)</td>
<td>0</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>12 (7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Renal disease</td>
<td>8 (2%)</td>
<td>0</td>
<td>0</td>
<td>4 (5%)</td>
<td>2 (2%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ulceration/amputation</td>
<td>4 (1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>4 (2%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Death</td>
<td>5 (1%)</td>
<td>0</td>
<td>0</td>
<td>1 (1%)</td>
<td>4 (2%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Differences between trajectory groups tested in χ² (categorical) and one-way ANOVA analyses (continuous variables).
clinical information beyond that recorded in the clinical databases was not available; as the data were de-identified, this problem could not be overcome. Assessing the potential relevance of lifetime glycemic control for the risk of complications, with the exception of retinopathy, is therefore difficult. Further, we lacked information about outcomes for those who were lost to follow-up immediately after the transition from pediatric care, for whom we consequently have no information about glycemic control trajectory or complication rates. This could account for the discrepancy between the standardized mortality ratio we estimated and that based on a population-based dataset in Western Australia (1.7 for men, 10.1 for women). Although glycemic control for most of the participants had been suboptimal throughout their lives, the SDR rate was low, but consistent with the recent report that 3.7% of young people (14–30 years old) with type 1 diabetes in Norway required laser therapy within 20 years of the onset of diabetes.16

A number of factors contribute to a higher risk of diabetes-related complications, including genetic susceptibility and cardiovascular risk factors (such as smoking, higher body mass index, greater waist:hip ratio, hyperlipidaemia, hypertension). Data on these factors were not available, and the omission of these known confounders from our analyses is a major limitation of this study. The duration of follow-up varied between individuals, and a shorter period of follow-up during adulthood may have led to misclassification of trajectory category. Cohort studies that assess individuals from diagnosis to death could overcome this limitation, but would be possible only for population-based registries or in large, multicentre cohort studies.

As the study period was broad, we also assessed the effect of era of diagnosis on SDR outcome (data not shown). While SDR was more common among those diagnosed prior to the publication of the DCCT findings (1994), the effect was not independent of the collinear higher glycemic control that commenced before contemporary target-based practice.

Our report describes the risk of diabetes-specific microvascular complications in a cohort of Australian adults who were diagnosed with type 1 diabetes during childhood. It is the first to assess clinical outcomes according to glycemic control trajectory between childhood and adulthood, and is the largest to use all available metabolic data from the diagnosis of type 1 diabetes onwards, with a longer duration of follow-up than reported elsewhere. In the absence of an Australian population-based registry of individuals with type 1 diabetes, this data linkage study facilitated assessment of the effects of glycemic control during the paediatric and adult periods. From this novel perspective, we found that, after adjusting for duration of diabetes (a non-modifiable factor), HbA1c level throughout the course of life was independently associated with the risk of retinopathy in adulthood; the predictive effects of paediatric and adult HbA1c levels were equivalent. However, as severe retinopathy commenced during the third decade of life in our cohort and most people had similar glycemic control levels in childhood and adulthood, the contribution of metabolic memory (the concept that hyperglycaemia appears to have a chronic rather than an acute effect on the development of complications)4 from the paediatric period was integral to this risk.

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Competing interests: No relevant disclosures.

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