The Transatlantic HbA1c gap: differences in glycaemic control across the lifespan between people included in the US T1D Exchange Registry and those included in the German/Austrian DPV registry

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Abstract

Aim To compare HbA1c levels across the lifespan in people with type 1 diabetes in the USA with those in Germany/Austria, and to examine potential differences in HbA1c levels between sexes, insulin delivery methods and minority status.

Methods Data were extracted from the US T1D Exchange Registry (n=18,381 participants from 73 sites) and from the German/Austrian Prospective Diabetes Follow-up Registry, the DPV (n=32,643 participants from 362 sites). Mean HbA1c was calculated for each year of age for individuals aged ≤25 years, and at 2-year age intervals for individuals aged >25 years. Curves for mean HbA1c by age were estimated using locally weighted scatterplot smoothing. HbA1c differences between registries, sexes, insulin delivery methods, and minority status were assessed by age group using multiple linear regression.

Results In both registries, mean HbA1c increased by ~11 mmol/mol (1.0%) between the ages of 9 and 18 years, although at quite different absolute levels: from 66 mmol/mol (8.2%) to 77 mmol/mol (9.2%) in the T1D Exchange Registry, and from 56 mmol/mol (7.3%) to 66 mmol/mol (8.2%) in the DPV. Sex differences were observed in the DPV only. In the T1D Exchange Registry, injection users had higher mean HbA1c than pump users across the lifespan, whereas in the DPV higher HbA1c levels in injection users were observed in the age groups 6 to <12 years, 12 to <18 years, and 30 to <50 years (P < 0.001). Minority status was significantly associated with higher HbA1c in most age groups in both registries.

Conclusions Significant differences in HbA1c were noted between the USA and Germany/Austria, with disparities more pronounced in early childhood through to young adulthood. Further studies should identify causes for these disparities.

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Introduction

For individuals with type 1 diabetes, optimal glycaemic control is essential to reduce the risk of acute and long-term complications. Treatment guidelines from the International Society for Paediatric and Adolescent Diabetes (ISPAD) as well as from the American Diabetes Association (ADA), the...
What’s new?

• Data from the TID Exchange Registry (T1DX) have shown that only few individuals with type 1 diabetes meet HbA1c targets, and that glycemic control has worsened in adolescents over recent years.

• Although a similar increase in HbA1c on reaching adolescence was observed, young people in the German/Austrian DPV registry had HbA1c levels that were 11 mmol/mol (1.0%) lower compared with young people included in the T1DX.

• Comparison of the two contemporary diabetes cohorts showed large discrepancies in glycemic control between developed Western countries, and highlights the need for increased efforts to improve care and particularly to lower HbA1c in young people with type 1 diabetes, especially those included in the T1DX.

German Diabetes Association (DDG), the Austrian Diabetes Association (ÖDG) and the Austrian working group for paediatric endocrinology and diabetesology (APEDÖ) set target HbA1c levels of < 53 or 58 mmol/mol (7.0% or 7.5%) [1–4]. However, studies from various regions of the world have demonstrated that individuals with type 1 diabetes, especially adolescents and young adults, often do not meet HbA1c targets [5–8].

The TID Exchange Registry (T1DX) in the USA and the Prospective Diabetes Follow-up Registry, the DPV, in Germany and Austria are two well-established consortia of diabetes centres that document treatment and outcome of individuals aged ≥25 years; individuals aged <25 years [T1DX, n=28 (0.2%); DPV, n=94 (0.3%)], were combined into one group, as were those aged ≥75 years [T1DX, n=139 (0.8%); DPV, n=636 (n=1.9%)]. Minority status was defined based on race/ethnicity for the T1DX (majority: non-Hispanic white; minority: black non-Hispanic, Hispanic or Other minority) and for the DPV (majority: non-Hispanic white; minority: Hispanic, non-Hispanic black, Other minority)

The analysis cohort included 51,024 individuals of all ages with type 1 diabetes for at least 1 year. The T1DX cohort included 18,381 individuals from 73 paediatric and adult endocrinology clinics in 34 US states, and the DPV cohort included 32,643 individuals from 362 specialized diabetes centres in Germany and Austria. Detailed information on the two registries can be found in Miller et al. [6] and Schwandt et al. [8].

Demographic and clinical data were obtained from medical records. We analysed the most recent HbA1c value between 1 April 2015 and 1 July 2016, with all values having been mathematically standardized to the Diabetes Control and Complications Trial (DCCT) reference range of 21–43 mmol/mol (4.1–6.1%) using the multiple-of-the-mean transformation method [10].

Table 1 Participant characteristics

|                | DPV (n=32,643) | T1DX (n=18,381) | P* |
|----------------|----------------|----------------|----|
| Age, years     | 15 (12, 20)    | 17 (13, 33)    | <0.001 |
| Duration of diabetes, years | 7 (4, 11) | 9 (6, 17) | <0.001 |
| Diagnosis year ≥2010, n (%) | 15,700 (48) | 5,132 (28) | <0.001 |
| Male sex, n (%) | 17,127 (52) | 9,125 (50) | <0.001 |
| Obesity, n (%) | 4,347 (14) | 3,472 (20) | <0.001 |
| Minority status*, n (%) | 5,398 (17) | 2,991 (17) | 0.316 |
| HbA1c, mmol/mol | 62 ± 16 | 69 ± 18 | <0.001 |
| %               | 7.8 ± 1.5     | 8.5 ± 1.7     | <0.001 |
| Total daily insulin dose per kg bodyweight | 0.80 (0.62, 1.00) | 0.75 (0.58, 0.94) | <0.001 |
| Pump use, n (%) | 14,759 (49) | 11,340 (63) | <0.001 |
| CGM use, n (%)  | 2,103 (6)    | 3,516 (20)    | <0.001 |

CGM, continuous glucose monitoring; T1DX, T1D Exchange Registry.

Data are presented as median (interquartile range), percentage, or mean ± SD. *P values are obtained from Wilcoxon or chi-squared test and are adjusted for multiple testing using the Bonferroni–Holm method. *Minority status: based on ethnicity (non-Hispanic white vs other ethnicities) for T1DX and migration background for DPV.
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Statistical methods

Characteristics of the study cohorts are given by registry (Table 1) and stratified by registry and age group (<6 years, 6 to <12 years, 12 to <18 years, 18 to <30 years, 30 to <50 years, ≥50 years; Table 2) as median (lower, upper quartile) and mean ± s.d. for asymmetrically and symmetrically distributed continuous variables, respectively, or as percentages. Unadjusted comparisons of cohort characteristics between registries were performed using Wilcoxon tests for continuous variables and chi-squared tests for percentages.

Curves of mean HbA1c by age were estimated using locally weighted scatterplot smoothing. The optimal smoothing parameter was selected using the corrected Akaike information criterion. Respective curves of mean HbA1c by age were estimated for boys/men and girls/women and for pump users and injection users.

Differences in HbA1c levels between the registries were assessed using a linear regression model stratified by age group and adjusted for sex, duration of type 1 diabetes, obesity, pump use and continuous glucose monitoring (CGM) use. Results are presented as adjusted mean differences between the T1DX and DPV with corresponding 95% CIs. Additional linear regression models were used to assess the difference in HbA1c within registries between sexes (adjusted for duration of diabetes, obesity, minority status, pump use and CGM use), between injection and pump users (adjusted for sex, duration of diabetes, obesity, minority status and CGM use), and between minority and non-minority status (adjusted for sex, duration of diabetes, obesity, pump use and CGM use).

The percentage of individuals achieving HbA1c levels <58 mmol/mol (7.5%) and <53 mmol/mol (7.0%) was tabulated by registry. The ISPAD, ADA and DDG HbA1c target for children and adolescents aged <18 years was <58 mmol/mol (7.5%) for the time period analysed [1–3], whereas the Austrian APEDÖ recommended an HbA1c target of <53 mmol/mol (7.0%) [4]. The ADA set an HbA1c target of <58 mmol/mol (7.0%) for adults, whereas the DDG recommended the same target HbA1c for adults as for children [<58 mmol/mol (7.5%)].

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Two-sided P values <0.05 were considered statistically significant. The Bonferroni–Holm correction was applied to adjust P values for multiple comparisons.

Ethics

Data collection was approved by the institutional review boards at the clinics participating in the T1DX or DPV study.
and by the ethics committee at Ulm University. Informed consent from the participants was obtained according to the requirements of the institutional review boards.

**Results**

Participant characteristics by registry are shown in Table 1. The median (lower, upper quartile) age was 15 (12, 20) years in the DPV and 17 (13, 33) years in the T1DX, and the median duration of diabetes was 7 (4, 11) and 9 (6, 17) years, respectively. Participant characteristics by age group (Table 2) revealed longer duration of type 1 diabetes in the T1DX than in the DPV in all age groups (all $P < 0.001$) except for the age group <6 years ($P=0.662$). In the T1DX, use of insulin pump therapy ranged between 59% (18 to <30 years) and 66% (6 to <12 years), whereas in the DPV pump use was most frequent in the youngest age group (89%) and least frequent in adults aged ≥50 years (29%). CGM use was higher in the T1DX compared with the DPV in all age groups (all $P < 0.001$).

In both registries, mean HbA1c increased by ~11 mmol/mol (1.0%) between ages 9 and 18 years, although at quite different absolute levels: from 66 mmol/mol (8.2%) to 77 mmol/mol (9.2%) in the T1DX, and from 56 mmol/mol (7.3%) to 66 mmol/mol (8.2%) in the DPV. HbA1c decreased in young adults, with a steeper slope in the T1DX, followed by plateaus at similar levels between the ages of 30 and 50 years. Beyond age 50 years, HbA1c gradually declined in both registries, although the decline was steeper in the DPV (Fig. 1). HbA1c was significantly lower (all $P < 0.02$) in the DPV compared with the T1DX in all age groups except for the age group 30 to <50 years (adjusted $P=0.198$; Table 3).

**Differences between sexes**

In the T1DX, no significant sex differences were observed (data not shown). In the DPV, HbA1c was higher in women than in men in the age group 18 to <30 years [adjusted mean difference 2 mmol/mol (95% CI 0, 3) or 0.1% (95% CI 0.0, 0.3); $P=0.006$] as well as in individuals aged ≥50 years [adjusted mean difference 2 mmol/mol (95% CI 1, 3) or 0.2% (95% CI 0.1, 0.3%); $P=0.002$].

**Differences between pump and injection users**

In the T1DX, mean HbA1c was higher in injection users than in pump users across the lifespan (Fig. 2a). The differences in mean HbA1c were significant for all age groups between 6 and <50 years after adjustment for sex, duration of diabetes, obesity, minority status and CGM use (Table 3). In the DPV, the largest difference in mean HbA1c between pump and injection users was observed in adults aged <50 years (Fig. 2b). Adjusted linear regression revealed significantly higher HbA1c in injection vs pump users in the age groups 6 to <12 years, 12 to <18 years, and 30 to <50 years, but there were no differences in HbA1c between treatment regimens in the other age groups (Table 3).

**Differences between minority and non-minority status**

In the T1DX, individuals with ethnic minority status had higher adjusted mean HbA1c than non-Hispanic white individuals in all age groups except for the age group <6 years (all $P < 0.001$; Table 3). In the DPV, significant differences between individuals with and without migration background were found for adolescents and adults aged 6 to <30 years and ≥50 years (Table 3).

**FIGURE 1** Mean most recent HbA1c by age (1-year intervals for individuals aged ≤25 years, 2-year intervals for individuals aged >25 years). Solid and dashed lines represent locally weighted scatterplot smoothing curves for the T1D Exchange Registry (T1DX) and the German/Austrian Prospective Diabetes Follow-up Registry (DPV), respectively. Grey areas represent corresponding 95% CIs.
| Age group | T1DX vs DPV | T1DX Injection vs pump | DPV Injection vs pump | T1DX Minority: yes vs no | DPV Minority: yes vs no |
|-----------|-------------|------------------------|-----------------------|--------------------------|-------------------------|
|           | Adjusted difference (95% CI) | Adjusted difference (95% CI) | Adjusted difference (95% CI) | Adjusted difference (95% CI) | Adjusted difference (95% CI) |
| <6 years  | 10 (9, 11) mmol/mol | 0.9 (0.9, 1.0)% | <0.001 | 1 (-1, 4) mmol/mol | 0.1 (-0.1, 0.4)% | 0.321 | 0.458 | 2 (1, 5) mmol/mol | 0.2 (-0.1, 0.4)% | 0.204 |
| 6 to <12 years | 10 (10, 11) mmol/mol | 1.0 (0.9, 1.0)% | <0.001 | 4 (3, 5) mmol/mol | 0.3 (0.2, 0.4)% | <0.001 | <0.001 | 4 (2, 5) mmol/mol | 0.3 (0.2, 0.4)% | <0.001 |
| 12 to <18 years | 11 (10, 11) mmol/mol | 1.0 (0.9, 1.0)% | <0.001 | 6 (5, 7) mmol/mol | 0.6 (0.5, 0.7)% | <0.001 | <0.001 | 6 (4, 7) mmol/mol | 0.5 (0.4, 0.6)% | <0.001 |
| 18 to <30 years | 7 (6, 8) mmol/mol | 0.6 (0.5, 0.7)% | <0.001 | 5 (4, 7) mmol/mol | 0.5 (0.3, 0.6)% | <0.001 | <0.001 | 6 (5, 8) mmol/mol | 0.6 (0.4, 0.8)% | <0.001 |
| 30 to <50 years | 0.198 | 0.198 | 0.198 | 0.2 (1, 4) mmol/mol | 0.2 (0.1, 0.3)% | 0.007 | <0.001 | 5 (3, 7) mmol/mol | 0.2 (0.1, 0.3)% | <0.001 |
| ≥50 years  | 1 (0, 2) mmol/mol | 0.25 | 0.025 | 1 (0, 2) mmol/mol | 0.1 (0.0, 0.2)% | 0.256 | 0.662 | 7 (4, 9) mmol/mol | 0.6 (0.4, 0.8)% | <0.001 |

CGM, continuous glucose monitoring; T1DX, TID Exchange Registry.
Difference in HbA1c given as estimated mean with 95% CI.

*Adjusted for duration of type 1 diabetes, sex, obesity, insulin delivery method (injections vs pump use), CGM use, and minority status.
†Adjusted for duration of diabetes, sex, obesity, CGM use and minority status.
‡Adjusted for duration of diabetes, sex, obesity, CGM use and minority status.
§P values adjusted for multiple testing.
Percentage of individuals achieving HbA1c targets

Among individuals in the DPV aged <6 years, 6 to <12 years and 12 to <18 years, 59%, 41% and 39%, respectively, achieved the ISPAD HbA1c target of <58 mmol/mol (7.5%); the respective percentages in the T1DX were lower (26%, 22% and 16%). In all three adult age groups, the percentage of individuals with HbA1c values <58 mmol/mol (7.5%) or <53 mmol/mol (7.0%) was higher in the DPV than in the T1DX (Table 2).

Discussion

In this cross-sectional lifespan comparison, significant differences in HbA1c were noted between two diabetes registries, with disparities more pronounced in early childhood through to young adulthood. The difference in HbA1c levels between pump and injection users was larger in the USA than in Germany and Austria, whereas differences in HbA1c levels between the sexes were found in Germany and Austria only. The higher HbA1c in young people in the USA compared to Germany/Austria may be related to systemic differences in access to medical care, diabetes education, provider prescribing practices, regulatory approval and insurance coverage of advanced technologies; as well as differences in patient self-management including adherence to treatment regimen, eating patterns, nutrient content of meals or snacks, and level of physical activity [11–14]. The high percentage of insulin pump use in the adult participants in the T1DX is in part attributable to the fact that the adults who receive their care at specialized diabetes clinics are more likely to be offered and interested in diabetes technology. This may not be representative of pump use in the general adult population with type 1 diabetes in the USA.
In both the USA and Europe, quarterly follow-up of people receiving type 1 diabetes care is recommended. A DPV study in individuals with type 1 diabetes aged <20 years reported a mean ± SD of 4.8 ± 2.5 visits per year [15]. In adults, the median HbA1c testing frequency was 8 (5; 9) times per 2 years, with 64% of the individuals being categorized as undergoing ‘frequent’ HbA1c testing (at least seven HbA1c measurements per 2 years) [16]. Transition from paediatric to adult care is a crucial time, however, and is often associated with deterioration of metabolic control [17–19]. In a T1DX survey of young adults aged 18 to <30 years who had already transitioned to adult care, 21% of the respondents reported a gap of >6 months between paediatric and adult diabetes care [17]. A DPV study even indicated that 60% of individuals with type 1 diabetes transitioning from paediatric to adult care had a period of >1 year between the last paediatric care visit and the first adult care visit [18].

Limitations of the present study are that the methods of data collection differ between the two registries and that HbA1c was not measured in a central laboratory. Nevertheless, all the HbA1c values were DCCT-standardized. In addition, a previous joint T1DX and DPV analysis in the paediatric population showed that differences in HbA1c were not attributable to differences in laboratory methods [20]. The DPV database comprises 70–90% of all potential paediatric individuals with type 1 diabetes in Germany and Austria, whereas it is not population-based for adults. All individuals in Germany and Austria are covered by statutory (90%) or private health (10%) insurance [21]. The T1DX includes a sample of specialized diabetes clinics in the USA, and uninsured individuals are probably under-represented in the cohort [6]; therefore, it is possible that HbA1c levels in the USA are underestimated, especially in adults, who are more likely to visit general practitioners/primary care settings to obtain prescriptions for diabetes treatment supply. Another limitation of this cross-sectional study is that it did not account for the period of pump or injection use, which could diminish the ability to detect differences in HbA1c between the insulin delivery methods. As the US concept of race/ethnicity is not transferable to Germany, minority status based on race/ethnicity for the T1DX and migration background for the DPV was used instead. Although the two definitions do not capture the same minority groups, previous comparisons between young people in the T1DX vs the DPV found minority status to be associated with worse glycaemic control [6,22]. In adults, however, migration background might be under-reported in the DPV database, and it represents a very heterogeneous group of individuals (e.g. older adults of German ancestry who were expelled after the end of World War II from various Eastern and Central European territories that had been occupied or annexed by Nazi Germany, or migrant workers mainly from Southern Europe who moved to Germany in the 1950s to 1970s).

Despite these limitations, the data provide a contemporary picture of glycaemic control across the lifespan in two large cohorts. Both cohorts report a consistent elevation in HbA1c with adolescence, but HbA1c was ~11 mmol/mol (1.0%) higher at all ages in the T1DX as compared to the DPV in paediatric care, whereas HbA1c is more similar in the two registries after the age of 30 years. It is concerning that, unlike HbA1c levels in young people in the DPV, HbA1c in those in the T1DX has not improved since the report of 2010–2012 data [9,22]. Further research to determine the causes of health outcome-related disparities between registries is critical to inform the design of quality improvement interventions, clinical trials of new treatment approaches, and innovative technologies/therapeutics to improve glycaemic control and patient-centred outcomes on both continents.

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**Competing interests**

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