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International benchmarking in type 1 diabetes:

Large difference in childhood HbA1c between 8 high-income countries but similar rise during adolescence

-A quality registry study

Short running title: Similar HbA1c pattern between countries

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Author Contributions

J.A., R.H., R.W.H., U.S., K.A. contributed to the study concept and design. J.M.H., J.A., R.W.H. and U.S. did the statistical analyses. J.A., U.S. and K.A. had the primary

responsibility for writing the paper. J.M.H., D.C., J.S., T.Sk., E.F.R., D.M.M., T.K., M.F., N.H.B., A.K.D., K.M., T.St., S.E.H., S.F., S.J.K., N.F., R.A., D.H., B.R.M., K.D.J., M.C., R.H., R.W.H. and J.T.W. contributed with data, reviewed and revised subsequent versions of the manuscript. J.M.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Abstract

Objectives To identify differences and similarities in HbA1c levels and patterns regarding age and gender in eight high income countries.

Subjects 66,071 children and adolescents below18 years of age with type 1 diabetes for at least 3 months and at least one HbA1c measurement during the study period.

Methods Pediatric Diabetes Quality Registry data from Austria, Denmark, England, Germany, Norway, Sweden, US and Wales were collected between 2013 and 2014. HbA1c, gender, age and duration were used in the analysis.

Results Distribution of gender and age groups was similar in the eight participating countries. The mean HbA1c varied from 60 to 73 mmol/mol (7.6 to 8.8%) between the countries. The increase in HbA1c between the youngest (0-9 years) to the oldest (15-17 years) age group was close to 8 mmol/mol (0.7%) in all countries ($p<0.001$). Females had a 1 mmol/mol (0.1%) higher mean HbA1c than boys ($p<0.001$) in seven out of eight countries.

Conclusions In spite of large differences in the mean HbA1c between countries, a remarkable similarity in the increase of HbA1c from childhood to adolescence was found.

Keywords Type 1 diabetes, children, adolescents, HbA1c, quality registry

Introduction

Type 1 diabetes mellitus is one of the most common chronic diseases among children and adolescents and the incidence has increased during the last decades [1]. It is well known that poor metabolic control, measured as HbA1c, increases the risk of micro- and/or macrovascular complications [2]. The Diabetes Control and Complication Trial (DCCT) showed that intensive therapy delays the onset of long-term complications and slows their progression [3]. Several subsequent studies have confirmed that improved metabolic control in type 1 diabetes decreases the risk of complications [4,5]. Furthermore, the type 1 diabetes population also has a higher mortality rate than the general population, and risk for mortality increases with poorer metabolic control [6].

International Society for Pediatric and Adolescent Diabetes (ISPAD) and American Diabetes Association (ADA), suggested a target HbA1c of < 58 mmol/mol (<7.5%) as the target for metabolic control in children and adolescents [7-9] at the time of the study, but national guidelines have since then argued for an even lower target value of 48 mmol/mol (6.5%) [10], referring to newer treatment regimens with reduction of risk for severe hypoglycemia. A high proportion of children and adolescents do not reach the treatment target, especially during adolescence [11,12]. Furthermore, a gender-dependent difference in metabolic outcome has been described, with females showing poorer glycemic control both in childhood and during adolescence [13,14].

With an aim to improve quality of care, track changes with time, and allow comparison between centers, several national diabetes registries have been established since the late 1990s. Comparison of registry data between countries has generated continuous interest over the past years, and has identified differences between countries as well as among centers within the same country [15,16].

A recent study has demonstrated a considerable difference in mean HbA1c among, and variation across centers within eight high income countries [17,18] . To try to better understand this difference, the present study aimed to identify differences and similarities in HbA1c levels and patterns regarding age and gender in these countries.

Methods

Study Design and Participants

The study design has been described in detail previously [17]. To summarize, anonymized data from six registries/audits on children with type 1 diabetes, according to ISPAD guidelines, were used. The registries/audits represent eight western high-income countries: Sweden from the Swedish Pediatric Diabetes Quality Registry (SWEDIABKIDS), Denmark from the Danish National Diabetes Registry (DanDiabKids), Norway from the Norwegian Childhood Diabetes Registry (NCDR), England and Wales from the National Paediatric Diabetes Audit (NPDA), Germany and Austria from the Prospective Diabetes Follow-up Registry (DPV), and USA from the T1D Exchange (T1DX). Except for T1DX, which is a clinic-based registry, all other registries are population-based registries with coverage of more than 80% of the respective countries' population of children with type 1 diabetes (table 1).

There is slight discrepancy in study population compared to the study by Charalampopoulos et al [17] due to different inclusion criteria. In this study, the inclusion criteria were: age <18 years, and type 1 diabetes for at least 3 months and at least one HbA1c measurement during the study period in 2013 (except in England and Wales where data were collected between April 2013 and March 2014). Glycemic control was assessed by level of HbA1c. The last

available HbA1c value over the study period was used for each child. We excluded children with missing HbA1c values (N=4096 [6%]). The final sample consisted of 66,071 children with type 1 diabetes.

All reported HbA1c values are in accordance with the International Federation of Clinical Chemistry (IFCC) [19] (mmol/mol). Corresponding HbA1c in National Glycohemoglobin Standardization Program (NGSP) units (%) are given in parenthesis. At the time of the study, nationally agreed target values for HbA1c were different between participating countries (Table 1).

Actual age at last registered HbA1c was used. Age at onset was registered for all children and used for calculation of actual diabetes duration. The following groupings of age and diabetes duration were used: 0-9 years old, 10-14 years old and 15-17 years of age; < 2 years, 2-5 years and > 5 years duration (Table 2).

The study was approved by the individual registry/audits in each country with ethical approval to collect patient data.

Statistical analysis

The Mann-Whitney U test and the Kruskal-Wallis test were used for unadjusted comparisons of continuous variables between two and more than 2 groups, respectively. Categorical variables were analyzed by the Chi-square test.

The Bonferroni-Holm method was applied to adjust p-values for multiple testing.

HbA1c by year of age stratified by country was depicted by nonparametric local regression smoothing (LOESS).

Multiple linear regression models were used to compare HbA1c levels between countries adjusted for duration of diabetes, age group, and gender. An additional regression model

including the interaction between country and age group as covariate was implemented to compare differences in pubertal HbA1c increase between countries. Furthermore Holm-Tukey`s method was used to account for multiple comparisons in regression models. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

This international benchmarking study includes registry data on HbA1c values from 66,071 patients across eight high income countries. The sample size varied between countries from 22,503 (England) to 1,376 patients (Wales) (Table 1). Missing data on HbA1c varied between 0.2 % in Sweden and 16.8 % in the USA. Mean age at onset differed from 6.9 to 7.7 ($p<0.001$) years and the mean diabetes duration ranged from 5.1 to 6.2 years ($p<0.001$). In the total population, the mean age at onset was 7.4 (± 3.9) and the mean diabetes duration 5.4 years (± 3.8). There were slightly more males than females in all countries (Table 1).

After adjustment for age, diabetes duration and gender, the mean HbA1c in the included countries showed a range of 60-73 mmol/mol (7.6-8.8%), ($p<0.001$) (Table 3). After adjustment for age and diabetes duration, the difference in HbA1c in males among most pairwise country comparisons (i.e. each country was compared with the other participating countries one by one) was significant ($p<0.01$). Exceptions (i.e. not significant) included Austria and Denmark vs. Germany, and England vs. USA. Among females, the HbA1c difference among most pairwise country comparisons (i.e. each country was compared with the other participating countries one by one) also was significant ($p<0.01$), with the exceptions (i.e. not significant) being Austria and Denmark vs. Germany, England vs. Wales, and USA vs. Wales, respectively. Females had a 1 mmol/mol (0.1%) higher mean HbA1c than males ($p<0.001$) in all countries except for Wales where no difference was seen in mean Hba1c. After adjustment for diabetes duration and gender, an increase in HbA1c with increasing age was seen in all countries (Table 3). Notably, the differences in HbA1c between

countries were found in each of the three age groups. The difference in HbA1c between the youngest vs. the oldest age group was 8 mmol/mol (0.7%) in all countries except for Germany 7 mmol/mol (0.6%) and Norway 9 mmol/mol (0.8%) (Table 3). The increase in HbA1c with increasing age in all countries is shown in Figure 1 using non-parametric regression of smoothing (LOESS). The slope of the curve becomes steeper at approximately 8-10 years of age regardless of the country`s baseline HbA1c level at age 8. The increase in HbA1c from childhood to adolescence is significant in all countries ($p<0.001$).

Discussion

In the present study, we found that the effect of age and gender on HbA1c is remarkably similar across eight high income countries and independent of the mean HbA1c for the population. Specifically, we found that HbA1c was higher in older children with an increase of approximately 8 mmol/mol (0.7 %), being very similar across all countries and independent of the adjusted mean HbA1c. The difference of 1 mmol/mol in HbA1c rise between Germany, Norway and the rest of the countries is of no clinical significance although it probably would be statistically significant depending on the large number of patients in each registry.

The differences in HbA1c between countries could not be explained by differences in age and gender. Regardless of the distribution of age groups and gender the differences in HbA1c between countries are the same. A somewhat unexpected finding was that the difference in mean HbA1c between males and females was minimal with a magnitude of no clinical importance.

The reason for the higher HbA1c with increasing age has been described earlier in a multinational study [20], and the cause for this could be multifactorial. It could be due to biological and behavioral differences during adolescence [11,21], attitudes among caregivers and clinic setup [22,23], socioeconomic differences [24], and/or family factors [24,25]. Such differences are

all equally important to improve care and should be taken into account together. For example, Sweden has the same increase in HbA1c with age as the other countries, in spite of showing a lower overall mean HbA1c after the development of a nationwide program of continuous quality improvement [23]. In countries with a low HbA1c in younger age groups compared to others, the HbA1c in the oldest age group was correspondingly low. As the difference in HbA1c between countries was the same in all age groups, some factors seem to influence the overall care in all countries rather than being a result of a more effective treatment in a certain age group. It was striking that teenagers in Austria, Denmark, Germany and Sweden seemed to have the same HbA1c level as the youngest age groups, i.e. preschool children, in England, Wales and US. The well-known increase in HbA1c during adolescence [12] seems to be the same in all countries.

Other groups have published longitudinal HbA1c data by age. In Scotland, a report from 2001 found a similar age pattern: HbA1c levels were significantly higher in older children (age 10-15 years 80 mmol/mol (9.5%) vs. other ages 73 mmol/mol (8.8%), $P < 0.001$) [26]. Clements et al has shown the same pattern from longitudinal data for T1D Exchange [27]. However, Mochizuki et al did not find lower HbA1c in the younger age group in Japan [28].

Since the difference in HbA1c existed over all age groups, national targets of HbA1c could have influenced the results. Sweden had the lowest target, and also the lowest HbA1c in all age groups. National targets thus seem to be important for the mean national HbA1c. Lowering targets may be one way to improve pediatric diabetes care [29]. USA lowered their target to < 58 mmol/mol (<7.5%) in 2014, England and Wales to <48 mmol/mol (<6.5%) in 2015 and Sweden to <48 mmol/mol (<6.5%) in 2017. ISPAD has lowered the target to <53 mmol/mol (<7.0%) in 2018 [30]. Future follow-up of national HbA1c comparisons will show if this results in a corresponding decrease in HbA1c. Nevertheless, our study indicates that the

increase of 8 mmol/mol (0.7%) during adolescence seems to be independent of national targets and mean HbA1c.

Apart from national targets, there may be differences in the approach to treatment in the different countries and also different approaches to technology such as pumps, number of injections per day, continuous glucose monitors etc. National improvement programs like the program in Sweden [31] and national tariffs in England [32] can be expected to further improve the outcome.

Our study should be interpreted within the context of its limitations. We do not have data on insulin regimes, socioeconomic status or comorbidity and therefore we do not know whether it could explain some of the observed variation. We also do not have data on severe hypoglycemia or episodes of DKA. The European registries are population-based while data from the US, although being the largest pediatric type 1 diabetes dataset available in the US, was based on a selective group of diabetes clinics[12]. The proportion of patients with short duration of diabetes is very low in the US T1D Exchange registry, which could explain some of the HbA1c differences observed between that registry and those of other countries. Another limitation is that the dataset originates several years back. However, recent data from the US indicate a rise in HbA1c in all pediatric age groups [33], while it has gone down in the UK [34].

In conclusion, we found a remarkable similarity in the increase of HbA1c from childhood to adolescence in spite of large differences in the mean HbA1c between countries. Variation in national targets for HbA1c may have contributed to this difference. It seems important to develop multidisciplinary diabetes care teams that set a low HbA1c target during childhood and adolescence. International benchmarking projects are essential in highlighting similarities and differences in the treatment of children and adolescents with type 1 diabetes and give the possibility to share knowledge between countries. Further research needs to focus on factors

contributing to the observed differences between countries, such as the impact of HbA1c targets, background populations', dietary habits, physical activity and health care providers' attitude.

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Country	Patients, n	Patients with HbA1c, n	Age at onset, years (SD)	Diabetes duration, years (SD)	Female, %	Target value for HbA1c mmol/mol (%)	National coverage
Austria	1597	1583	7.3 (4.0)	5.1 (3.7)	45	53 (7.0)	~80%
Denmark	2074	1894	7..7 (3.9)	5.1 (3.6)	49	55 (7.2)	~100%
England	22503	21401	7.6 (4.0)	5.3 (3.7)	48	58 (7.5)	>95%
Germany	20580	20187	7.4 (3.9)	5.2 (3.7)	48	58 (7.5)	~95%
Norway	2416	2321	7.5 (3.8)	5.2 (3.5)	48	<58 (<7.5)	>95%
Sweden	6540	6524	7.4 (4.0)	5.5 (3.8)	47	52 (6.9)	~98%
USA	13081	10877	6.9 (3.7)	6.2 (3.4)	48	< 6 years 69 (8.5) 6-12 years 64 (8.0) > 13 years 58 (7.5)	N/A
Wales	1376	1284	7.5 (3.9)	5.2 (3.6)	48	58 (7.5)	>95%
Total	70167	66071	7.4 (3.9)	5.4 (3.8)	48		

Table 1. Data on the number of patients, the number of patients with HbA1c, age at onset, diabetes duration and proportion of females from the eight participating registries, target value for HbA1c for each country in the year 2013 and national coverage for each registry.

Duration group	Austria %	Denmark %	England %	Germany %	Norway %	Sweden %	USA %	Wales %
<2 years	24	20	21	23	20	21	5	22
2-<5years	31	36	33	32	34	31	39	32
>=5 years	45	44	46	45	46	48	56	46

Table 2. The proportion of patients in the groups stratified by diabetes duration < 2 years, 2-5 years and >=5 years.

Country	mean -HbA1c mmol/mol and % (95% CI)					
	Total	**Males**	**Females**	**0-9 years**	**10-14 years**	**15-17 years**
Austria	63 (62-64) 7.9 (7.8-8.0)[a,b]	63 (61-64) 7.9 (7.7-8.0)[c]	64 (63-65) 8.0 (7.9-8.1)[e]	58 (56-59) 7.4 (7.3-7.5)	61 (60-62) 7.7 (7.6-7.8)	66 (65-68) 8.2 (8.1-8.4)
Denmark	64 (63-64) 8.0 (7.9-8.0)[a]	63 (62-64) 7.9 (7.8-8.0)[c]	64 (63-65) 8.0 (7.9-8.1)[e]	58 (57-60) 7.5 (7.4-7.6)	61 (60-63) 7.7 (7.6-7.9)	66 (65-68) 8.2 (8.1-8.4)
England	72 (71-72) 8.7 (8.6-8.7)	71 (70-71) 8.6 (8.5-8.6)[d]	72 (72-73) 8.7 (8.7-8.8)[f]	66 (65-66) 8.2 (8.1-8.2)	70 (69-70) 8.5 (8.4-8.5)	74 (74-75) 8.9 (8.9-9.0)
Germany	62 (61-62) 7.8 (7.7-7.8)[b]	61 (61-62) 7.7 (7.7-7.8)[c]	62 (62-63) 7.8 (7.8-7.9)[e]	57 (57-58) 7.4 (7.4-7.5)	60 (59-60) 7.6 (7.5-7.6)	64 (63-64) 8.0 (7.9-8.0)
Norway	66 (65-67) 8.2 (8.1-8.3)	66 (65-67) 8.2 (8.1-8.3)	67 (66-68) 8.3 (8.2-8.4)	60 (58-61) 7.6 (7.5-7.7)	65 (64-66) 8.1 (8.0-8.2)	69 (68-70) 8.4 (8.4-8.5)
Sweden	60 (59-60) 7.6 (7.5-7.6)	59 (58-60) 7.5 (7.5-7.6)	60 (60-61) 7.6 (7.6-7.7)	54 (53-55) 7.1 (7.0-7.2)	58 (57-59) 7.5 (7.4-7.5)	62 (61-63) 7.8 (7.7-7.9)
USA	71(70-71) 8.6 (8.5-8.6)	70 (70-71) 8.5 (8.5-8.6)[d]	71 (71-72) 8.6 (8.6-8.7)[g]	65 (64-66) 8.1 (8.0-8.2)	70 (69-70) 8.5 (8.4-8.5)	73 (72-73) 8.8 (8.7-8.8)
Wales	73 (72-74) 8.8 (8.7-8.9)	73 (72-75) 8.8 (8.7-9.0)	73 (72-75) 8.8 (8.7-9.0)[f,g]	68 (66-70) 8.4 (8.2-8.5)	72 (70-73) 8.7 (8.5-8.8)	76 (74-77) 9.1 (8.9-9.2)

Table 3. Linear regression models (pooled model) Total and age group HbA1c data are adjusted for age, duration and gender. Gender HbA1c data are adjusted for age and duration. [a-g] describe non-significant differences in HbA1c between countries with the same letter.