EPIDEMIOLOGY OF TYPE 1 DIABETES IN CHILDREN IN HUNGARY

PhD Thesis

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INTRODUCTION

Diabetes mellitus with onset in childhood represents one of the most frequent chronic diseases in children and young adults. The disease is associated with a significant burden to society and patients because most cases require lifelong treatment with insulin as well as access to day-to-day monitoring and treatment of complications and because the disease confers increased risk of severe late complications such as renal failure, blindness, amputations, heart disease, and stroke.

It is estimated that on an annual basis some 76,000 children aged 14 years and under develop type 1 diabetes worldwide. In 2010, some 480000 children worldwide were estimated to have type 1 diabetes. 23% of these children come from Europe. Apart from the extremely wide global variation in incidence, there were two major characteristics of the epidemiology of childhood type 1 diabetes over the last few decades of the twentieth century. Incidence increased in most countries and this trend was accompanied by a shift in the age of onset to the youngest age group (0 to 4 years).

A substantial percentage of children, who are currently being diagnosed with type 1 diabetes, present with potentially life-threatening ketoacidosis. Ketoacidotic episodes are still the most common causes of hospitalisation and deaths in children with type 1 diabetes and also seem to influence the longer term clinical course of type 1 diabetes.

Although some studies have found that the clinical presentation at onset has become less severe with time; there is no clear evidence that the prevalence of diabetic ketoacidosis at time of diagnosis has decreased over the past years; in fact with increasing incidence of type 1 diabetes reported to be most remarkable in youngest children, an actual increase is anticipated.

AIMS

Our study had two main aims. First to analyse the incidence of type 1 diabetes in the age group 0–14 years in Hungary for the period 1989–2009, second to ascertain the spectrum of severity of presentation, the prevalence of diabetic ketoacidosis at diagnosis of diabetes, and the potential predictors of DKA.

I. INCIDENCE OF TYPE 1 DIABETES IN CHILDREN (0-14 YEARS) IN HUNGARY

1. Incidence trends over time

To predict future trends.

2. Gender, age-group specific incidence

To analyze gender difference and age-group specific incidence.

3. Seasonality

To investigate the seasonal pattern at onset of type 1 diabetes.

4. Regional differences in incidence

To investigate any regional differences among counties in Hungary

II. CLINICAL CHARACTERISTICS OF TYPE 1 DIABETES AT TIME OF DIAGNOSIS IN HUNGARIAN CHILDREN (2002-2009)

1. Clinical and biochemical characteristics at time of diagnosis during 2002-2009

To investigate gender and age group specific differences. To separately evaluate disease onset in very young children (<2 years of age).

2. Diabetic ketoacidosis

To investigate the frequency of DKA at type 1 diabetes onset, to analyze temporal trends.

To compare clinical characteristics of children presenting with and without DKA.

To identify predictors of diabetic ketoacidosis in newly diagnosed children (0-14years)

Study design

The area of Hungary is divided into 19 counties, of which 18 were included. Budapest, the capital, and the surrounding region were excluded from our study because historically we have found that the ascertainment level was low. In Hungary, prospective registration as part of the EURODIAB Study started in 1989. The establishment of the Hungarian Childhood Diabetes Register has previously been described in detail. Children with newly diagnosed type 1 diabetes under the age of 15 years are prospectively registered. All cases diagnosed between 1 January 1989 and 31 December 2009 were included in the analysis. In Hungary, children with new-onset diabetes aged 0–14 yr are hospitalized in paediatric departments at the time of diagnosis. Hospital case records served as the primary source and we used the list

of children who attended diabetes summer camps as an independent secondary source of ascertainment. These camps, organized by trade unions and later by charity organizations, were open to all diabetic children. Capture-recapture method was used to estimate the completeness of case registration. All denominators for incidence calculations were provided annually by the Central Bureau of Statistics.

I. INCIDENCE OF TYPE 1 DIABETES IN CHILDREN (0-14 YEARS) IN HUNGARY

Statistical methods

Annual end-year population estimates were used as denominators for calculation of rates. Age- and sex-standardized incidence rates were obtained using the direct method with a standard population consisting of equal numbers of children in each of the six subgroups defined by age group (0–4y, 5–9y and 10–14y) and gender. Poisson regression models were used to assess time trends in incidence. Models with terms for age group, gender and calendar year were fitted. Predictions for future new cases until 2030 were made by extrapolating rates using the annual percentage increase in incidence in each age/sex subgroup estimated from the Poisson regression model.

Results

A total of 3432 patients (1777 boys; 1655 girls) under the age of 15 years were registered during the observation period. The average standardised incidence rate was 12.5 (95%CI 12.0-12.9) per 100000 per annum over the 21 years, 12.6 (95% CI 12.0-13.2) in boys and 12.3 (95% CI 11.72-12.9) in girls. The age-specific incidence rates were 8.8 (95% CI 8.2-9.5), 13.5 (95% CI 12.7-14.3) and 15.1 (95% CI 14.3-15.8) per 100000 person years in the 0-4, 5-9 and 10-14 year age groups, respectively.

The incidence increased from 7.7 (95%CI 6.3-9.0) per 100000 person years in 1989 to 18.2 (95%CI 15.7-20.9) in 2009 (Figure 1).

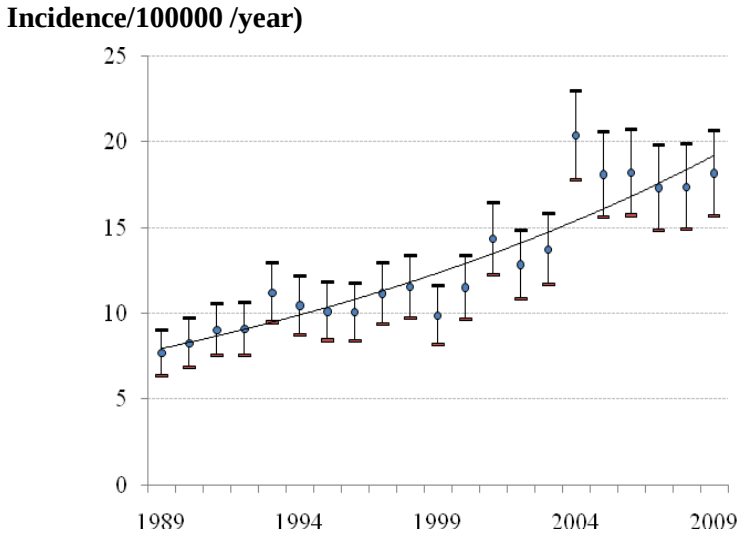

Figure 1. Age-standardised incidence rate (with 95% confidence intervals) for type 1 diabetes in children aged 0-14 years in Hungary for each year in the period 1989-2009 with fitted log-linear trend.

Table 1 Summary of Poisson regression analyses fitted to data in 3 age groups, 2 sexes and 21 years

	Model		**Likelihood ratio test on last model term**			**Goodness-of-fit test**		
		-2log L	χ^2	***df***	**P**	χ^2	***df***	**P**
0	A+S+A•S	1020.37				381.97	120	<0.001
1	A+S+A•S+Y	784.34	236.04	1	<0.001	145.93	119	0.05
2	A+S+A•S+Y+Y^2	784.23	0.11	1	0.74	145.82	118	0.04
3	A+S+A•S+Y+Y•A	769.19	15.14	2	0.001	130.79	115	0.15
4	A+S+A•S+Y+Y•A+Y•S	763.37	5.82	1	0.016	124.97	116	0.27
5	A+S+A•S+Y+Y•A+Y•S+Y•A•S	760.36	3.01	2	0.22	121.96	114	0.29

A - Age, S - Sex,
Y - linear term in year,
Y^2 - quadratic term in year,
Y•A - Interaction between Y and A

Results of the Poisson regression analysis are summarized in Table 1. This analysis demonstrated a highly significant linear trend in incidence over the 21-year period (line 1, Table 1). Interestingly, year 2004 is an outlier with its unusually high incidence rate. There was also evidence of a significant difference in the trends between age groups (line 3, Table 1) and between genders (line 4, Table 1) with rates increasing faster in the younger age-groups and in boys.

Figure 2 shows that the increase was evident in both genders with higher rates for boys (5.1%, 95% CI 4.3-5.9; p<0.001) compared to girls (3.7%; 95% CI 2.9-4.6; p<0.001). Boys showed faster rates of increase in incidence of type 1 diabetes in all three age groups than did girls, but only in the oldest age-group was this difference significant (P=0.004). Assuming that the rates of increase observed in 1989-2008 continue, by 2030 the number of newly diagnosed children aged 0-14 years in Hungary is predicted to be 2460 with a distribution of 31% being in the 0-4 year, 38% in the 5-9 year and 31% in the 10-14 year age groups. The predicted age-specific incidence rates are, respectively, 56 per 100000, 59 per 100000, and 43 per 100000 for the three age groups.

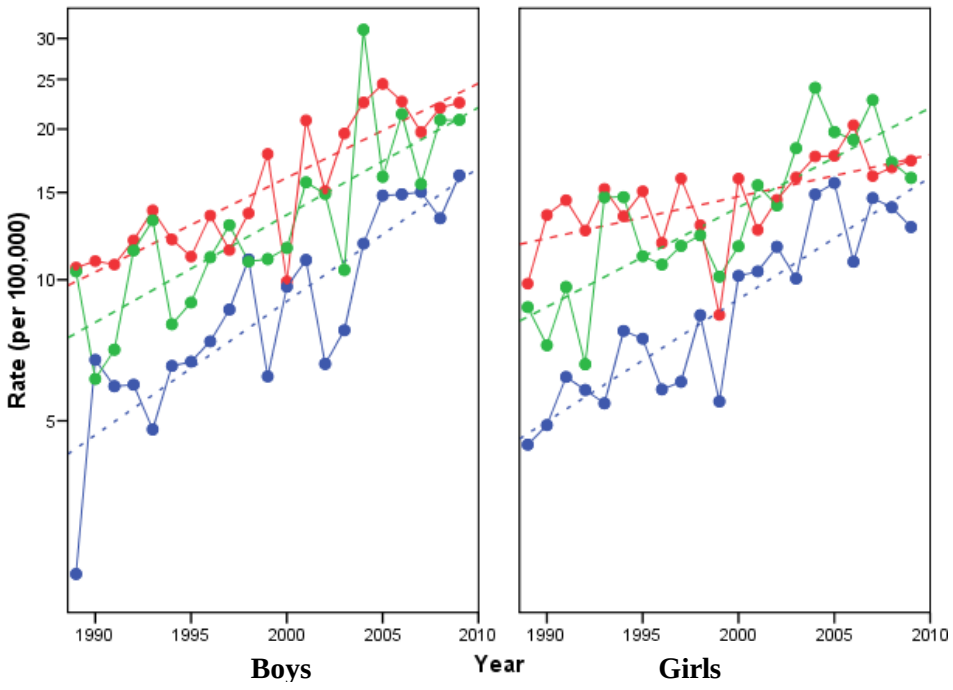

Figure 2 - Time trends in age-specific incidence rates in boys and girls plotted on a logarithmic scale for each year in the period 1989-2009.

II. CLINICAL CHARACTERISTICS OF TYPE 1 DIABETES AT ONSET IN CHILDREN AGED 0-14 YEARS IN HUNGARY

Study design

Prospective registration of laboratory and clinical data at diagnosis as part of the Hungarian Childhood Diabetes Register has started in January 1, 2002. All children with new-onset type 1 diabetes aged 0-14 years diagnosed between 1 January 2002 and 31 December 2009 were involved in our study. Information regarding the clinical presentation, duration (given as number of days) of symptoms prior to diagnosis observed by a parent (or reported by a child) and preceding infection were recorded. Weight and height at diagnosis was documented. BMI (kg/m2) was expressed as body mass index standard deviation score (BMI-SDS) based on the national standard data of the longitudinal growth study by Joubert et al. Biochemical data were obtained before administering intravenous fluids or insulin at the hospital. Ketoacidosis was defined as a blood pH less than 7.3. Ketoacidosis was defined as pH<7.3 and severe DKA as pH≤7.1. Positive family history was defined as having a first-degree relative with type 1 diabetes.

Statistical methods

For normally distributed variables data were summarized as mean values ± standard deviations (SD). Unequally distributed results expressed as median and interquartile range (IQR) were analyzed by Kruskal-Wallis and Mann-Whitney U tests. Continuous variables were compared by the independent sample Student`s t- or one-way analysis of variance tests; categorical variables, using cross tabulation calculation. Univariate analyses were followed by a dichotomous (DKA yes/no) logistic regression model with forward, stepwise elimination methods, including all variables that showed $p<0.10$ on univariate analysis.

Results

Between 1 January, 2002 and 31 December, 2009, a total of 1558 newly diagnosed children (828 boys; 730 girls) were identified with type 1 diabetes. The mean age at diabetes diagnosis was 8.6±3.9 years (range 0.4-14.9); girls were younger (8.3±3.8 years; p=0.02) as compared to boys (8.8±4.0 years). The mean blood glucose concentration was 26.5±11.9 mmol/l (range 6.9-140mmol/l), the mean glycated haemoglobin (HbA1c) was 11.9±2.6 % (range 5.6-25.8%) at the time of diagnosis.

DKA (pH<7.3) was identified in 35.1% of the children (n=547), 10.6% of the children had severe DKA. Patients with ketoacidosis at onset were younger and one-quarter of them had an acute infection at presentation (Table 2). Prevalence did not differ significantly between boys and girls (34.7% vs 35.6%; p=0.72).

Table 2 Clinical and biochemical characteristics of children with newly diagnosed type 1 diabetes according to age groups

	0-4 years	**5-9 years**	**10-14 years**	**p**
n (%)	351 (22.5)	553 (35.5)	654 (42)	<0.001[1]
Male (%)	176 (50)	283 (51)	369 (56)	NS
Duration of symptoms (days)	9 (7-19)	14 (7-21)	21 (7-28)	<0.001[1,2] 0.02[3]
BMI-SDS	-1.04±1.3	-0.54±1.1	-0.51±1.0	<0.001[1,2]
Blood glucose (mmol/l)	29.4±13.1	26.0±11.0	25.4±11.6	<0.001[1,2]
HbA1c (%)	10.9±2.2	12.0±2.6	12.3±2.6	<0.001[1,2]
pH	7.26±0.16	7.31±0.13	7.31±0.13	<0.001[1,2]
DKA, pH<7.30 (%)	46.4	33.2	30.7	<0.001[1,2]
Severe DKA, pH<7.10(%)	17.2	9.8	7.9	<0.001[1,2]

Data are mean±SD or median (interquartile range) or frequency
[1]0-4yr vs 5-9 yr; [2]0-4yr vs 10-14 yr; [3]5-9yr vs 10-14 yr

Children aged <2 years had a significantly higher rate of DKA at presentation compared to children 2.0-4.9 years (59.3% vs 41.2%; p=0.003). The prevalence of severe acidosis was found in 25.3% of children <2 years (14.0% in 2.0-4.9 years of age; p=0.01).
Although there was some year to year fluctuation, the overall rate of DKA remained very similar (Figure 3) during the study period.

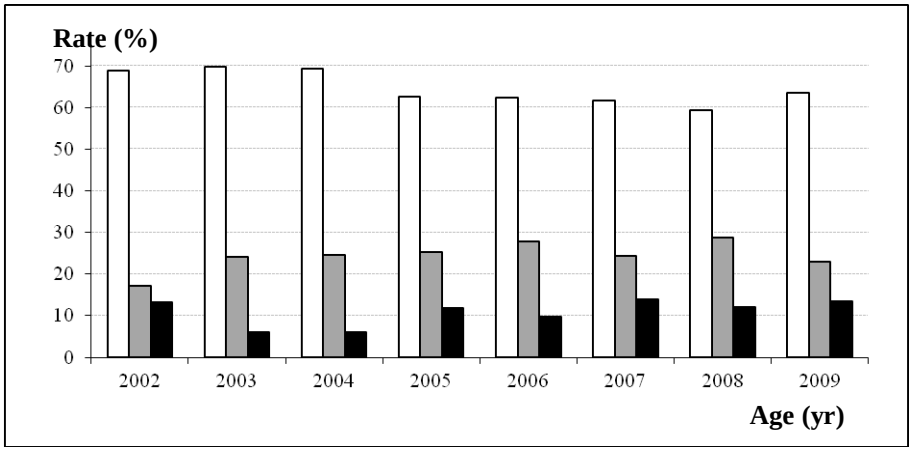

Figure 3 **-** Annual rate of DKA in children with type 1 diabetes aged 0-14 years at time of diagnosis in Hungary (2002-2009). *White column: no DKA; grey column: mild to moderate DKA (7.1≤pH<7.3); black column: severe DKA (pH<7.1*

Using logistic regression analysis, we found that children <2 years of age had two times the risk of presenting in diabetic ketoacidosis as children 10-14 years of age. Children with lower BMI-SDS are more likely to present in diabetic ketoacidosis. Higher blood glucose and a history of infection were associated with an increased risk of diabetic ketoacidosis. Our study failed to show a significant association with a family history of type 1 diabetes.

THESIS

I. INCIDENCE OF TYPE 1 DIABETES IN CHILDREN (0-14 YEARS) IN HUNGARY

1. Incidence trends

- With the overall incidence rate of 12.5 per 100000 per year, Hungary belongs to the medium incidence geographical regions. The most important finding of the present study was that the annual increase (3.6%) of type 1 diabetes during 1979-1998 has continued

further at an even higher rate (5.3%) in the last 11 years with no evidence of levelling off. The increase follows a linear trend with random fluctuations

- Extrapolation of incidence rates would suggest that by 2030 the predicted number of new cases is 2460 but this change is not shared evenly between the age groups with incidence of type 1 diabetes in the youngest age group expected to increase by 3.5 times in both sexes compared with a factor of 2.5 in boys and 1.5 in girls in the oldest age group. Our model suggests that in 2030 the percentage distribution of new cases across the three age-groups will be more uniform at 31% (0–4 years), 38% (5–9 years), and 31% (10–14 years), with the excess of new cases in the 5–9 year age range being most apparent in boys.

2. Gender, age-group specific incidence

- The increases in incidence seen in the present study were evident in both genders. Boys showed faster rates of increase in incidence in all three age groups than did girls, but only in the oldest age-group was this difference significant.
- From the beginning of the study period our results demonstrated a greater relative increase in incidence in the youngest children (6.2%), particularly in boys, compared to the increase in 5-9 years old (4.9%) and 10-14 years old children (3.3%). In spite of the rapid increase of the 0-4 year-old age group, the incidence rates (total and sex-specific) remain lowest in the youngest children and highest in 10-14 year-old children. The difference in incidence among the age groups, however, seems to be diminishing; at the end of the study period the incidence in the 5 to 9 year age group has now reached that of the 10 to 14 year age group, particularly in females.

3. Seasonality

- Our study confirms the well-known seasonality of type 1 diabetes at diagnosis with a peak during winter (January) and a trough during summer (June). Seasonal variation was most apparent in 10-14 year-old children and absent in youngest children, possibly due to a lower number of cases in this age group.

4. Regional differences in incidence

- Disease maps demonstrated marked geographical variation in incidence within Hungary. There were indications that counties in the Western part of Hungary tend to have higher incidence rates, while counties in the Eastern part had lower rates than the overall average, however the rate of increase failed to show any significant difference.

Continued registration of incidence is of paramount importance to recognize long term tendencies, which may provide clues to the environmental exposures behind these trends. Furthermore, appropriate planning of services and resources are necessary to meet the need for the increased number of children diagnosed with diabetes. The rising incidence has far reaching effects beyond the diabetes teams: in schools, the community and other components of the healthcare system that these children use currently and in the future.

II. CLINICAL CHARACTERISTICS OF TYPE 1 DIABETES AT TIME OF DIAGNOSIS IN HUNGARIAN CHILDREN

1. Clinical and biochemical characteristics at time of diagnosis during 2002-2009

- The duration of clinical symptoms in type 1 diabetes is short, about 14 days and one third of the children were reported to have symptoms for less than 7 days. Polyuria and polydipsia remain the most common symptoms noted in 89% of the children. The majority of children have no family history of type 1 diabetes. Biochemical characteristics at diagnosis were in agreement with those from other studies: the mean blood glucose level was 26.5±11.9 mmol/l, mean HbA1c was 11.9±2.6 % and mean pH 7.30±0.14.
- The clinical symptoms at onset did not differ significantly between groups with regard to age and gender. Youngest children had gross hyperglycaemia with mean blood glucose close to 30 mmol/l, while HbA1c was lowest in children aged 0-4 years, indicating a shorter duration of hyperglycaemia in this age group.

2. Diabetic ketoacidosis

- Overall 32% of children aged <15 years presented with ketoacidosis at the time of T1DM onset. In Hungary, the frequency of DKA is high and has not changed over the years despite the increase in incidence of T1DM. Our study showed an increased frequency and severity of DKA at presentation in the younger age groups and a reduction with increasing age. Nearly half of the young children 0-4 years of age presented in DKA at diagnosis compared to about one third in children aged 10-14 years. We observed a conspicuously severe clinical decompensation at onset of type 1 diabetes in children less than 2 years of age; about 60% of them presented with diabetic ketoacidosis and one fourth presented with impaired consciousness. Patients with ketoacidosis at onset had a significantly lower BMI-SDS, higher mean blood glucose and mean HbA1c level and one-quarter of them had

an acute infection at presentation. The occurrence of DKA was less frequent in children with a first degree relative of type 1 diabetes.

- As expected, DKA was more prevalent in younger age groups. Our study showed that children <2 years old had two times the risk of presenting in diabetic ketoacidosis as children aged 10-14 years. Furthermore, higher blood glucose, lower BMI-SDS and a history of infection were significantly associated with an increased risk of DKA. Neither a history of T1DM in a first-degree relative nor the duration of symptoms predicted a diagnosis of new-onset diabetes before progression to DKA.

In Hungary despite considerable improvements in diabetes therapy, no significant decline was observed in the prevalence of onset DKA over the past 8 years. This finding suggests that the general public is still not familiar with the signs and symptoms of type 1 diabetes, parents seek medical attention late, and that can lead to more profound metabolic decompensation, especially in younger children. The unacceptably large proportion of diabetic children with a high blood glucose, glycated haemoglobin, dehydration and ketonuria indicate a relatively severe metabolic decompensation at the time of diagnosis and call for further improvement in the diagnostic acumen of the paediatric community, as well. The very young children, in whom clinical presentation is more acute and early diagnosis may be difficult are particularly vulnerable.

From an epidemiological perspective, further improvements should be made in the educational programs to increase the sensitivity of parents, child carers and physicians to the early signs of hyperglycaemia

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