Increased Incidence of Type 1 Diabetes among Children without Changes of Clinical Characteristics at Onset

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Abstract

Aim
The incidence of childhood type 1 diabetes mellitus (T1DM) is increasing in many countries. The aim of this study was to study demographic and disease related variables between childhood T1DM with onset during lower incidence periods compared to onset during higher incidence periods.

Methods
Data collected from medical records of children with onset of T1DM 1993-1998 (n=48) were compared with data from children diagnosed 2011-2013 (n=51).

Results
The incidence of T1DM in our region was 35/100,000 children per year during 1993-1998 which increased to 65/100,000 per year 2011-2013 (p<0.001). All patients diagnosed in 1993-1998 were of Nordic origin whereas only 88.2% in the latter group (p=0.01). There was a difference between the groups with respect to initial use of intensive care (p=0.03), which was more common in the group with onset in 2011-2013. No significant differences were found between the groups regarding gender, family history of diabetes, age at diabetes diagnosis, duration of symptoms, weight loss, weight and height at admission to hospital, Body Mass Index (BMI), weight at discharge from hospital, blood pressure, vP-glucose, HbA1c, C-peptide, vB-pH, base excess, ketoacidosis, associated diseases like hypothyreosis and celiac disease, separated parents, patients’ use of alcohol or smoking.

Conclusion
The incidence of childhood diabetes in Helsingborg in southern Sweden has increased substantially in recent decades despite immigration from areas with lower diabetes risk. The causes for this, and the contribution of social, clinical and laboratory parameters at the onset are still unclear and need further investigation.

Keywords
Environmental Factors; Ethnicity; Incidence; Juvenile Onset Diabetes Mellitus; Migration; Type 1 Diabetes Mellitus

Abbreviations
BMI Body Mass Index
CI Confidence Interval
DM Diabetes Mellitus

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Received January 02, 2018; Accepted January 12, 2018; Published January 30, 2018

Citation: Charlotte Ekelund (2018) Increased Incidence of Type 1 Diabetes among Children without Changes of Clinical Characteristics at Onset. SF J Diabetes Endocrin 2:1.

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1. Introduction

The incidence of childhood onset diabetes has increased worldwide with Sweden having the highest incidence in the world next to Finland [1]. The highest recorded incidence rate in children younger than 15 years was 64.9 per 100,000 children in Finland 2006 and since then the incidence of T1DM seems to be levelling off in Finland [2], as well as in Sweden as indicated by a previous study [3]. However, a recently published study shows how the incidence of T1DM continues to increase in Sweden with an incidence rate of 48.8 per 100,000 children below the age of 15 years 2014-2015 [4]. International multicentre studies have reported a worldwide increase in incidence of 3% annually during childhood (0-14 years) since the 1980s with the highest relative increase in incidence in Europe found in children below the age of five years [5-7]. Nevertheless, a Swedish study states that the incidence in patients aged 15-34 years has increased as well [8] and is two to three times higher than previously reported [9].

T1DM is associated with auto antibodies against the insulin producing β-cells in the pancreas causing destruction of the β-cells [10]. Diabetes associated auto antibodies may be detectable years before overt disease. Over time the number of auto antibodies present in a given child usually increases and thus serves as a predictor for disease development [11-14]. Although the aetiology of T1DM is unknown, a combination of genetics and environmental factors is considered to cooperate. The most important genes contributing to T1DM susceptibility are located in the Human Leukocyte Antigen (HLA) class II locus on the short arm of chromosome 6. The HLA haplotype DR3-DQ2 and/or DR4-DQ8 are carried by more than 90% of children with T1DM [15, 16]. However, the presence of risk genes alone does not explain the appearance of T1DM. Approximately 5% of individuals with genetic predisposition progress to clinical disease by the age of 15 years [17]. Several different environmental factors and changes in lifestyle are proposed to trigger β-cell autoimmunity to initiate the progression to T1DM and may represent the causes of geographical differences and the increase in incidence [1, 18-20]. Viral infections (enterovirus, coxsackie B virus, cytomegalovirus, rotavirus, mumps, rubella and retroviruses), early exposure to cow’s milk formula as well as rapid growth and weight gain have all been implicated as potential risk factors in developing T1DM, whereas breast feeding and early vitamin D supplementation have been associated with reduced risk [18-20]. The geographical variation with higher prevalence of T1DM in northern countries, even within-country variation, and the seasonal variation with higher incidence during autumn and winter suggests that low sun exposure, i.e. low levels of vitamin D, and cold climate matter [6, 21]. Migrant research indicates that population groups who have moved to a high incidence area from a low incidence region show increased incidence of T1DM and points out the significance of environmental conditions. Changed food habits, with introduction of foreign food items to populations previously not used to them, have increased because of migration. This coincides with the increase in incidence of T1DM in Sweden and may be of importance [22]. Changes in our environment during the last decades might be the reason why more individuals have developed the disease, at a younger age and with less genetic susceptibility [23]. Therefore, better understanding of environmental factors and of the acute onset of the disease could lead to new possibilities to predict and prevent T1DM as well as to improved medical care.

The aim of this retrospective study was to determine possible differences in demographic and disease related variables between patients with T1DM with onset during childhood in 1993 to 1998, when the incidence was lower, and in 2011 to 2013, when the incidence was higher, in order to further highlight the characteristics of the acute
onset of childhood T1DM.

2. Methods

2.1 Study Design and Study Population

The study was performed as a retrospective observational study. Data collected from medical records of children and adolescents below the age of 18 with onset of T1DM between 1 January 1993 and 31 December 1998 (n=48) were compared with data from children and adolescents below the age of 18 diagnosed between 1 January 2011 and 31 December 2013 (n=51). The classification of T1DM was made by T1DM specific antibodies and clinical characteristics. All data were collected from a local registry and medical records at a single site, the Department of Pediatrics, Helsingborg Hospital, Sweden. The local registry was established in 1974 with incidence registration only until 1991 and thereafter with full personal identification making inclusion in this study possible. With the exception of missing data from the year 1992, the registry is complete. The 48 patients registered in 1993 to 1998 were thus the first patients with personal identification in the registry and the 51 patients registered in 2011 to 2013 were the last ones in the registry. This study procedure gave a maximum time interval between the two groups, which optimized the opportunity to find possible differences between the groups. The participants agreed to take part in the study by being sent an information letter and all chose to participate. Data were missing in three cases in the group from the 1990s, but in the latter group all patients were included.

Data were analysed regarding the acute onset of T1DM and gender, age at diabetes diagnosis, duration of symptoms, weight loss prior to diagnosis, weight and height at admission to hospital, BMI, weight at discharge from hospital, blood pressure, vP-glucose, HbA1c, C-peptide, vB-pH, base excess, ketoacidosis (pH < 7.30, base excess < -6) at onset, initial use of intensive care, associated diseases like thyroid gland disorders and celiac disease, auto antibodies, HLA-associated genetic diabetes risk and family history of diabetes but also factors like ethnicity, separated parents, patients’ use of alcohol and smoking. The incidence rate of newly diagnosed T1DM by years was calculated as an average of three years at a time from 1974 to 2013 except for 1992 due to missing data. Vital population statistics, for children and adolescents younger than 18 years, for these calculations were found on the website of Statistics Sweden [24].

2.2 Ethics

The study was approved by the Regional Ethical Review Board, Lund, Sweden, (Dnr 2006/599, 2013/693 and 2014/822) and the study was in accordance with the Declaration of Helsinki.

2.3 Statistical Analysis

The D’Agostino-Pearson test was used to examine normal distribution of data. Results that were normally distributed are presented as mean ± Standard Deviation (SD). The T-test was used for comparison between groups. The non-parametric variables, i.e. results not normally distributed, are presented as median and inter quartile range and the Mann-Whitney U-test was used for comparison between groups. Frequencies are presented as numbers and percent and were compared using Chi-square test or Fisher’s exact test in case of low numbers. A Poisson regression model was used to assess the effect of time (year) on the incidence rate of T1DM. Testing for trend was conducted by fitting three year periods as a continuous variable in the log-linear Poisson regression model with person-years as an offset. Predicted incidence and 95% confidence interval (CI) are presented. Statistical analyses were performed with IBM SPSS Statistics 22 for Windows (IBM Corporation, New York, NY, USA) and MedCalc® for Windows (version 13.0.4.0). P-values below 0.05 were considered statistically significant.

3. Results

The incidence of childhood T1DM in the area of Helsingborg has increased significantly (p<0.001) from the 1970s until 2013, which was assessed in a log-linear Poisson regression model as presented in Figure 1.

Figure 1: Incidence rate of Childhood Type 1 Diabetes by Years. Observed (Points) and Trend (Line) Rates with 95% Confidence Interval (Dashed Line) Predicted by a Poisson Regression Model
This study compared two groups of patients with diabetes diagnosed in 1993 to 1998, with a calculated incidence rate of 35 children and adolescents per 100,000 per year, and 2011 to 2013, with a calculated incidence rate of 65 children and adolescents per 100,000 per year. All patients in the group diagnosed in 1993 to 1998 were of Nordic origin. In the latter group only 88.2% were Nordics (p=0.01), whereas the others were immigrants from Serbia, Palestine, Iraq, Islamic Republic of Iran, Pakistan and Saudi Arabia, one child from each country. There was also a difference between the groups with respect to the initial use of intensive care (p=0.03), which was more common in the group with onset in 2011 to 2013. The prevalence of celiac disease was higher, but not statistically significant (p=0.06), in the group diagnosed in 2011 to 2013. No significant differences were found between the groups regarding gender, family history of diabetes, age at diabetes diagnosis, duration of symptoms, weight loss prior to diagnosis, weight and height at admission to hospital, BMI, weight at discharge from hospital, blood pressure, vP-glucose, HbA1c, C-peptide, vB-pH, base excess, ketoacidosis, associated diseases like hypothyreosis and celiac disease, separated parents, patients’ use of alcohol or smoking. The results are presented in Table 1.

Table 1: Comparison of Characteristics at the Acute Onset of Type 1 Diabetes between Two Groups Diagnosed in 1993 to 1998 (n=45) and 2011 to 2013 (n=51)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DM Diagnosis 1993-98 n = 45*</th>
<th>DM Diagnosis 2011-13 n = 51**</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/Male</td>
<td>16/29</td>
<td>20/31</td>
<td>0.87</td>
</tr>
<tr>
<td>Family history of DM (%)</td>
<td>26 (61.9) n=42</td>
<td>29 (56.9)</td>
<td>0.78</td>
</tr>
<tr>
<td>Nordics (%)</td>
<td>45 (100)</td>
<td>45 (88.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age at DM diagnosis (years)</td>
<td>10.2 (5.9-14.5)</td>
<td>9.1 (6.2-12.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>14.0 (7.0-21.0) n=44</td>
<td>11.5 (3.5-21.0) n=48</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>25 (75.8) n=33</td>
<td>30 (62.5) n=48</td>
<td>0.10</td>
</tr>
<tr>
<td>Weight at admission (kg)</td>
<td>31.2 (20.5-46.3) n=44</td>
<td>31.4 (20.8-39.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>Height at admission (m)</td>
<td>1.5 (1.3-1.7) n=32</td>
<td>1.3 (1.2-1.5) n=46</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>16.4 (14.8-18.3) n=32</td>
<td>16.4 (14.5-18.4) n=46</td>
<td>0.56</td>
</tr>
<tr>
<td>Weight at discharge (kg)</td>
<td>32.9 (19.1-46.3) n=24</td>
<td>33.5 (21.6-43.2) n=40</td>
<td>0.92</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>110.8±14.8 n=19</td>
<td>111.1±13.5 n=39</td>
<td>0.93</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>68.9±9.0 n=18</td>
<td>68.8±12.0 n=39</td>
<td>0.97</td>
</tr>
<tr>
<td>vP-glucose (mmol/l)</td>
<td>24.6±7.9 n=40</td>
<td>25.3±11.2 n=37</td>
<td>0.74</td>
</tr>
<tr>
<td>HbA1c IFCC (mmol/mol)</td>
<td>90±20.5 n=44</td>
<td>83±27.4</td>
<td>0.15</td>
</tr>
<tr>
<td>HbA1c NGSP (%)</td>
<td>10.4±4.0</td>
<td>9.7±4.7</td>
<td></td>
</tr>
<tr>
<td>C-peptide (nmol/l)</td>
<td>0.25 (0.17-0.31) n=31</td>
<td>0.23 (0.15-0.46)</td>
<td>0.98</td>
</tr>
<tr>
<td>vB-pH</td>
<td>7.38 (7.32-7.41) n=18</td>
<td>7.36 (7.34-7.37)</td>
<td>0.06</td>
</tr>
<tr>
<td>Base excess (mmol/l)</td>
<td>-1.0 (-6.7-0.7) n=43</td>
<td>-1.0 (-11.0-1.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Ketoacidosis (%)</td>
<td>14 (31.1)</td>
<td>16 (31.4)</td>
<td>0.98</td>
</tr>
<tr>
<td>Intensive care (%)</td>
<td>1 (2.2)</td>
<td>8 (15.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypothyreosis (%)</td>
<td>1 (2.3) n=44</td>
<td>0 (0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Celiac disease (%)</td>
<td>0 (0) n=43</td>
<td>5 (10)</td>
<td>0.06</td>
</tr>
<tr>
<td>Separated parents (%)</td>
<td>13 (29.5) n=44</td>
<td>7 (13.7)</td>
<td>0.10</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>0 (0) n=37</td>
<td>2 (3.9)</td>
<td>0.51</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>0 (0) n=42</td>
<td>1 (2)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The data are presented as mean ± SD, median (inter quartile range) or number (percent). DM: Diabetes Mellitus; IFCC: International Federation of Clinical Chemistry; NGSP: National Glycohemoglobin Standardization Program.

* n=45 unless otherwise noted
**n=51 unless otherwise noted
4. Discussion

The incidence of childhood T1DM has increased in many countries in recent decades. The main finding of this study is that the increase is also seen in the area of Helsingborg in southern Sweden despite immigration from areas with lower incidence rates of T1DM [1]. Even though the genetic background has changed within the population there has been significant increase in incidence rate in Helsingborg since the 1970s implicating that environmental factors are of importance. This is in line with what has been reported from the UK suggesting that changes in our environment during the last decades might be the reason why more individuals have developed the disease despite less genetic susceptibility [23]. However, a Swedish study has come to the conclusion, by studying parental country of birth, that geographical differences in childhood T1DM seem to be favoured by genetic susceptibility rather than by environmental factors [25]. Like food habits it is possible that even other environmental factors involved can be transferred from one region to another [25]. This finding is consistent with a previous study of Sardinian migrants in Italy suggesting heritage as an important determinant for T1DM in childhood [26]. Thus as reported, there has been a substantial increase in incidence of T1DM in children in Sweden and in many countries worldwide [1, 8]. The reason for the increase, and the contribution of genetic and environmental factors, is still unclear and under debate. By studying demographic and disease related characteristics at the acute onset we hoped to find clues to the aetiology of T1DM or environmental factors that might have changed over time and thus influenced the incidence of T1DM. However, with respect to social, clinical and laboratory parameters our study did not show any differences between the groups. The number of non-Nordics was higher in the latter group and the difference was statistically significant. It was interesting to note that the difference in ethnicity did neither influence the acute characteristics at onset of T1DM nor the incidence of the disease. The statistically significant difference in initial use of intensive care should not be overemphasized due to small numbers and to the fact that the indications for use of intensive care may have changed over time. The proportion of cases presenting with ketoacidosis was the same in both our groups, 31.1% respectively 31.4%. Similar to our data, a US study has found that the prevalence of ketoacidosis was stable over time with almost one-third presenting with ketoacidosis, but a higher prevalence associated with minority populations [27]. In our study three out of six children to immigrant parents presented with ketoacidosis at diagnosis in 2011 to 2013. It is reasonable to believe that the prevalence of ketoacidosis ought to be lower in the group diagnosed in 2011 to 2013 due to The Environmental Determinants of Diabetes in the Young (TEDDY) study diagnosing high risk individuals early by close follow-up [28]. In recent years the possibility of better knowledge and awareness of T1DM in the population might also affect the prevalence of ketoacidosis at the onset of T1DM presumably reducing the initial use of intensive care.

The prevalence of celiac disease was higher, but not statistically significant (p=0.06), in the group diagnosed in 2011 to 2013. Celiac disease is a common autoimmune disorder that shares the same genetic background as T1DM and occurs in T1DM with increasing prevalence. Concomitant occurrence of celiac disease and T1DM is 3-16% with a mean prevalence of 8% [29].

Previous studies have shown a more pronounced increase in incidence in the youngest age group, i.e. below the age of five, than among older children, adolescents and adults [3, 6, 7, 9]. This could however not be confirmed in our study, probably due to small numbers.

This study is examining children and adolescents with T1DM over time in the same geographical area. A strength of the study is that it consists of all available cases, i.e., no drop-outs, in our area for the studied periods. Despite this the numbers are small, which is a limitation of the study, and the study might therefore be underpowered. This can be the reason for the outcome, with just a few significant differences. It would have been desirable to investigate possible genetic differences and differences in diabetes associated auto antibodies between the groups. This was, however, not possible due to missing genetic and autoantibody data in the group diagnosed in the 1990s. Life events and residential area were studied, but the numbers were too small for any interpretation.

In conclusion, the incidence of childhood T1DM has increased despite immigration from areas with lower diabetes risk. The causes for this, and the contribution of genetic and environmental factors, are still unclear and not explained by this study and examination over time of characteristics at the start of the disease in our area. Hopefully, this study will be followed by examinations of larger populations to identify effective prevention methods for T1DM to stop the global increase in incidence.

5. Acknowledgements

We would like to acknowledge Helene Jacobsson, MSc, and Claes Ignell, MD, PhD, for skilful statistical assistance. We also wish to acknowledge the diabetes team...
at the Department of Pediatrics, Helsingborg Hospital. This study was supported by grants from the Stig and Ragna Gorthon Foundation [grant numbers 2014-1185, 2015-1262].

6. Declaration of Interest

Conflicts of interest: none.

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