RECENT INCIDENCE OF TYPE 1 DIABETES MELLITUS IN MONTENEGRO: A SHIFT TOWARD YOUNGER AGE AT DISEASE ONSET

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SUMMARY – In the last several decades, a great number of studies have pointed to a dramatic increase of type 1 diabetes mellitus (T1DM) incidence in the whole world, especially in younger age groups. Therefore, the aim of the study was to assess changes in the age distribution at onset of T1DM in Montenegro children aged <15 years during a 15-year period (1997-2011) and analyze the seasonal pattern. Primary case ascertainment was from diabetes register, secondary and tertiary independent data sources were hospital case records and register of children receiving free test strips in pharmacy. Standardized incidence rates were calculated using the Poisson regression. Case ascertainment was 100% complete using the capture-recapture method. The mean age-standardized incidence was 18.6/100,000 (95% CI: 13.0-24.1) from 2007 to 2011 compared with 13.4/100,000 (95% CI, 11.5-15.5) from 1997 to 2006. The incidence of T1DM increased predominantly in younger age groups. Relative increase of incidence per 5-year period was largest in boys aged 0-4 and 5-9 years: 64.7% (95% CI: 20.6-10.7; p=0.004) and 52.8% (95% CI: 16.9-88.8; p=0.004), respectively. Seasonality in monthly case counts of T1DM was apparent. The greatest number of cases were diagnosed during autumn and winter months. In conclusion, the onset of T1DM was found to occur at an ever younger age in Montenegro children. Our results indicated a seasonal pattern of the disease onset.

Key words: Diabetes mellitus, type 1; Child; Incidence; Epidemiology; Montenegro

Introduction

Two international childhood-onset type 1 diabetes registries (EURODIAB and DIAMOND) deal with research of the epidemiology of diabetes, which is necessary for understanding the etiopathogenesis of type 1 diabetes (T1DM). Application of standardized methods showed great variations in diabetes incidence rates, dramatic increase in the incidence of T1DM in the whole world, earlier clinical presentation of the disease, and seasonal variation¹. According to EURODIAB, in Europe the highest rates of childhood diabetes are found in Scandinavia and northwest Europe, with an incidence ranging from 57.4 cases/100,000 per year in Finland to the lowest rate of 3.9/100,000 in FYR Macedonia. The annual growth of incidence is 3.9% (1989-2003) and it is noticeable in all age groups, mostly in children aged 0-4 years (5.4%)²,³.

During the last twenty years, greatest changes in the incidence of T1DM occurred in the countries of Central and Eastern Europe, whereas Sardinia and north Europe countries except for Finland marked a plateau in the growth of T1DM incidence⁴.

During the 1996-2006 period, the incidence of childhood-onset T1DM among Montenegro children under 15 years of age was 13.4/100,000 per year. The annual increase rate for this period was 4.6%⁵.
Many registries describe seasonal variation in the date of T1DM diagnosis, with a note that the disease is most often diagnosed during winter months. This is associated with the number of sunny days, which is important for the synthesis of vitamin D and for seasonal infections.

The aim of this study was to examine changes in the age distribution at onset of T1DM in Montenegro children aged <15 years during a 15-year period (1997-2011) and to analyze the seasonal pattern of the disease diagnosis.

**Material and Methods**

**Geographical and population data**

Montenegro is located in South-Eastern Europe, with an area of 13812 km² and a population of 620,145 (according to the 2011 census), including 118,751 (19%) children in the 0-14 age group.

**Ascertainment**

Diabetes onset in children and adolescents aged <15 years was documented according to the EURODIAB criteria. All children living in Montenegro and diagnosed with T1DM from 1996 to 2011 were included in the study. They were admitted to the Institute for Sick Children, Podgorica, the only tertiary care children’s hospital in Montenegro. The register of children suffering from T1DM exists since 1982, but prospective registration as part of the EURODIAB study started in 2007. Hospital case records served as primary source of ascertainment. The National Public Health Institute diabetes register and register of children receiving free test stripes in the pharmacy were used as independent secondary and tertiary sources of ascertainment. Completeness of ascertainment was estimated with the capture-recapture method.

**Statistical analysis**

Children population was obtained from the 2003 and 2011 census data, as well as the mid-year population estimates for other years in the study, published by the Statistical Office of Montenegro (MONSTAT). Age and sex specific incidence rates were calculated from the number of new cases divided by the estimated number of person-years at risk in the respective age group.

### Table 1. Age and sex specific incidence rates of type 1 diabetes mellitus in Montenegro during 1997-2012

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age group (yrs)</th>
<th>1997-2001</th>
<th>2002-2006</th>
<th>2007-2011</th>
<th>Average percentage increase of incidence per 5-yr periods % (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>0-4</td>
<td>6.9 (1.2-15.0)</td>
<td>8.6 (-0.1-17.3)</td>
<td>17.9 (1.8-34.0)</td>
<td>64.7 (20.6-10.7)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>5-9</td>
<td>9.0 (4.9-13.2)</td>
<td>11.8 (0.2-23.4)</td>
<td>24.5 (9.3-39.8)</td>
<td>52.8 (16.9-88.8)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>15.9 (7.2-25.5)</td>
<td>23.8 (9.9-37.6)</td>
<td>23.0 (12.5-33.5)</td>
<td>17.9 (-10.0-45.8)</td>
<td>0.209</td>
</tr>
<tr>
<td></td>
<td>0-14*</td>
<td>10.4 (5.5-15.3)</td>
<td>14.3 (7.2-21.5)</td>
<td>21.5 (14.4-28.5)</td>
<td>35.3 (15.9-54.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>Girls</td>
<td>0-4</td>
<td>9.3 (5.2-13.4)</td>
<td>11.3 (3.0-19.6)</td>
<td>9.8 (4.2-15.5)</td>
<td>3.1 (-40.6-46.8)</td>
<td>0.888</td>
</tr>
<tr>
<td></td>
<td>5-9</td>
<td>11.6 (3.9-19.3)</td>
<td>25.2 (11.7-35.6)</td>
<td>23.5 (7.8-39.1)</td>
<td>31.1 (0.0-62.3)</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>12.0 (2.8-21.3)</td>
<td>17.2 (12.8-21.6)</td>
<td>14.8 (7.4-22.1)</td>
<td>10.0 (-24.2-44.2)</td>
<td>0.566</td>
</tr>
<tr>
<td></td>
<td>0-14*</td>
<td>10.8 (7.0-14.7)</td>
<td>17.3 (12.7-21.9)</td>
<td>15.4 (8.7-22.2)</td>
<td>17.6 (-2.7-37.9)</td>
<td>0.089</td>
</tr>
<tr>
<td>All</td>
<td>0-4</td>
<td>8.1 (4.9-11.2)</td>
<td>9.9 (3.1-16.6)</td>
<td>14.0 (3.7-24.4)</td>
<td>28.2 (-1.7-58.2)</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>5-9</td>
<td>10.3 (6.3-14.2)</td>
<td>18.3 (14.3-22.2)</td>
<td>24.0 (13.1-34.9)</td>
<td>40.6 (17.2-64.1)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>10-14</td>
<td>14.0 (6.9-21.1)</td>
<td>20.6 (15.0-26.2)</td>
<td>19.0 (12.4-25.6)</td>
<td>14.9 (-6.7-36.5)</td>
<td>0.177</td>
</tr>
<tr>
<td></td>
<td>0-14*</td>
<td>10.6 (7.2-14.0)</td>
<td>15.8 (11.7-19.8)</td>
<td>18.6 (13.0-24.1)</td>
<td>26.9 (12.9-40.9)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Incidence per 100 000 children per year in 5-year periods (95% CI) and mean percentage increase per 5-year periods; *age standardized incidence
group (0-14, 0-4, 5-9 and 10-14 years) for each sex. Confidence intervals were calculated assuming a Poisson distribution. Age and sex standardized incidence rates were obtained for the 0-14 age group using the direct method with the world standard population. Poisson regression models were also used to estimate the effects of sex, age (three age groups: 0-4, 5-9 and 10-14 years) and calendar time (three 5-year periods: 1997-2001, 2002-2006 and 2007-2011). Annual incidence rates were calculated from 1997 to 2011. The rates calculated from 1997 to 2006 were found to be identical to those previously published. Statistical analyses were performed using SPSS 17. The level of statistical significance was set at p<0.05.

**Results**

Overall ascertainment using the three independent sources and capture-recapture method was estimated to be 100% complete for the study period. The incidence rates according to sex, age group and calendar period are shown in Table 1. The incidence increased over the study period from 10.6/100,000 (95% CI: 7.2-14.0) in 1997-2001 to 18.6/100,000 (95% CI: 13.0-24.1) in 2007-2011. The mean percentage increase of incidence per 5-year period was 26.9%. There was a plateau from 2007 to 2011, with no increase in the incidence in that period (Table 2).

Two youngest age groups (0-4 and 5-9 years) had the highest relative increase of incidence. We found a steep increase in the incidence of T1DM in Montenegrin boys aged <5 years (64.7%) per three 5-year periods (Fig. 1). The mean annual incidence peaked during 2002-2006 at 25.2/100,000 (95% CI: 11.7-35.6) in 5- to 9-year-old girls and during 2007-2011 at 24.5/100,000 (95% CI: 9.3-39.8) in 5- to 9-year-old boys (Table 1).

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**Table 2. Newly diagnosed cases of type 1 diabetes mellitus and annual incidence per 100 000 population with 95 confidence interval (95% CI)**

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of cases</th>
<th>Annual incidence (boys and girls)</th>
<th>95%CI</th>
<th>Annual incidence (boys)</th>
<th>95% CI</th>
<th>Annual incidence (girls)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>28</td>
<td>21.8</td>
<td>13.7-30.0</td>
<td>25.3</td>
<td>13.2-37.5</td>
<td>18.0</td>
<td>7.29-28.82</td>
</tr>
<tr>
<td>2008</td>
<td>26</td>
<td>21.6</td>
<td>13.2-30.0</td>
<td>29.0</td>
<td>15.5-42.6</td>
<td>13.6</td>
<td>4.06-23.06</td>
</tr>
<tr>
<td>2009</td>
<td>14</td>
<td>10.8</td>
<td>5.1-16.5</td>
<td>14.6</td>
<td>5.6-23.7</td>
<td>6.8</td>
<td>0.07-13.56</td>
</tr>
<tr>
<td>2010</td>
<td>23</td>
<td>19.7</td>
<td>11.6-27.8</td>
<td>18.8</td>
<td>7.6-30.0</td>
<td>20.5</td>
<td>8.82-32.28</td>
</tr>
<tr>
<td>2011</td>
<td>23</td>
<td>18.8</td>
<td>11.1-26.6</td>
<td>19.5</td>
<td>8.4-30.6</td>
<td>18.1</td>
<td>7.36-28.83</td>
</tr>
</tbody>
</table>

Fig. 1. Time trends in age- and sex-specific incidence rates in the 1997-2012 period.
The mean age at onset for the entire study period was 7.9±3.9 years. The mean age at onset was 7.9±4.2 years in 2007-2001, 8.1±3.8 years in 2002-2006, and 7.6±3.9 years in 2007-2011 period. The mean age at diagnosis decreased during the study period, but not statistically significantly (p=0.685).

The number of cases according to months for all children is presented graphically in Figure 2. The greatest number of cases were diagnosed from October to March, i.e. in autumn and winter months.

**Discussion**

This study represents an updated analysis of epidemiological data from the Montenegro Childhood Diabetes Registry confirming the increasing incidence of childhood-onset T1DM over the 15-year study period. Two youngest age groups (0-4 and 5-9 years) had the highest relative increase. This is in accordance with other studies reporting the increasing incidence of T1DM mostly in younger age group, but is completely different from data reported in Croatia where the increase in the disease incidence ceased in the youngest children. Similar to some other studies, we found a steep increase in the incidence T1DM in Montenegro boys under five years of age. A slight predominance of male children is noted in the populations with a higher incidence of T1DM. This could mean that external factors affect male children more than female children and speed up the processes that lead to earlier clinical manifestation of diabetes.

The incidence of T1DM increased in Montenegro from 1997 to 2007, with a plateau of about 21.8/100,000 since 2007, followed by stable rates until 2011 (Table 2). Previously, stabilization of rates was observed from 2003 to 2006. Similar results were obtained in some high risk countries, which reached a plateau in the disease incidence and shift toward younger age at disease onset. According to some authors, the increase of T1DM incidence is the consequence of earlier clinical presentation rather than of global increase of incidence, earlier exposure to external factors for the development of T1DM, and faster progression of the subclinical disease process to overt diabetes. This points to the importance of those factors which are active in the prenatal and perinatal period, such as birth weight, maternal age, type of delivery, duration of breastfeeding, and virus infections, especially enteroviruses.

Data on early introduction of cow milk into diet as a risk factor for the onset of diabetes are controversial. Children with higher birth weight and born by an older mother are at a greater risk of having diabetes. In the last decade, women in Montenegro are forming their families much later, which can slightly contribute to the increase of T1DM incidence.

Hypönen et al. found that children from Finland who developed T1DM were heavier and taller than control children. According to the so called accelerator hypothesis, obesity and resistance to insulin stimulate the autoimmune process and earlier presentation of diabetes. In Sweden, there is a reversed diabetes incidence trend, starting in 2000, which is a result of preventive programs for suppression of obesity.

The most recent publication by Martinovic et al. shows that in Montenegro significant changes occurred in people's diet and that there is more frequent occurrence of obesity among schoolchildren. According to the latest International Obesity Task Force (OITF) reference, there are 17.6% of overweight children and 5.3% of obese children. Obesity is two times more frequent among Montenegro boys compared with girls (7.0% vs. 3.5%).

Climate in Montenegro is continental, Mediterranean and mountain. We investigated seasonal variation during the study period. The greatest number of cases were diagnosed during autumn and winter months. Seasonality in monthly case counts of T1DM is apparent in most EURODIAB centers, in all age groups and both sexes.

In conclusion, the results of this study indicated that T1DM incidence was still increasing in younger age groups, especially in boys aged 0-4 years. We need further research of the factors which have an impact.
on the increase of T1DM incidence. Epidemiological studies will contribute to better understanding of diabetes and better planning of health care for the children suffering from T1DM.

References


Sažetak

NOVI PODACI O INCIDENCIJI DIJABETESA TIPO 1 U CRNOJ GORI: BOLEST POČINJE U MLAĐOJ ŽIVOTNOJ DOBI

M. Samardžić, M. Martinović, M. Nedović-Vuković i M. Popović-Samardžić

Posljednjih desetljeća velik broj istraživanja ukazuje na dramatičan porast incidencije dijabetesa tipa 1 u cijelom svijetu, naročito u mlađim dobnim skupinama. Cilj ovoga istraživanja bio je obnoviti podatke iz prethodne studije, istražiti promjene u dobi pojavljivanja dijabetesa kod djece u dobi od 0 do 14 godina (1997.-2011.) i analizirati sezonski obrazac pojava bolesti. Kao prvi izvor poslužili su podaci iz registra oboljelih od šećerne bolesti, a kao drugi i treći izvor korištena su bolnička otpusna pisma i registar djece koja primaju besplatno test trake u ljekarnama. Za izračun standardizirane incidencije korišten je Poissonov regresijski model. Upotrebom metode capture–recapture pouzdanost podataka procijenjena je na 100%. Standardizirana incidencija za dobnu skupinu 0-14 godina bila je 18,6/100.000 (95% CI: 13,0-24,1) od 2007. do 2011. godine u usporedbi s incidencijom od 13,4/100.000 (95% CI: 11,5-15,5) od 1997. do 2006. godine. Incidencija dijabetesa tipa 1 rasla je pretežito u mlađim dobnim skupinama. Relativno povećanje incidencije u petogodišnjem razdoblju bilo je najveće kod dječaka dobnih skupina 0-4 i 5-9 godina: 64,7% (95% CI: 20,6-10,7; p=0,004) odnosno 52,8% (95% CI: 16,9-88,8; p=0,004). Izražen je sezonski obrazac, tj. bolest se najčešće dijagnosticira u jesenjim i zimskim mjesecima. U zaključku, dijabetes tipa 1 u Crnoj Gori dijagnosticira se kod djece sve mlađe dobi. Naši rezultati ukazuju na sezonski obrazac pojave bolesti.

Ključne riječi: Dijabetes melitus, tip 1; Dijete; Incidencija; Epidemiologija; Crna Gora