Original article

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Evidence for the increase in the incidence of type 1 diabetes in children aged 0-14 years in the Republika Srpska, 2001-2016

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Objective – The purpose of the study was to estimate the changes in the incidence trends of type 1 diabetes mellitus in children for the territory of the Republika Srpska (Bosnia and Herzegovina) during the period from 2001 to 2016. **Methods** – A retrospective technique was used to register all newly diagnosed cases of type 1 diabetes mellitus in children aged 0 to 14 years during the 2001 – 2016 period. The determination was based on the capture-recapture method, and was estimated to be 99%. **Results** – The average incidence of type 1 diabetes mellitus was estimated to be 11.0 cases per 100,000 during the 2001-2016 period. The annual increase in incidence was 14.2%. The highest incidence rates were recorded in 2015 (21.3 cases /100,000) and lowest in 2002 (4.7 cases /100,000). The largest incidence rate of 13.6% /100,000 was found in the oldest age group examined, from 10-14 years. **Conclusion** – The incidence rate of type 1 diabetes mellitus in children in the Republika Srpska was found to have a rising trend over the last 16 years. Considering the incidence rate of 11.0 cases /100,000, the Republika Srpska is in the group of regions with a medium risk for diagnoses of diabetes. Unfortunately, this trend seems to be even more pronounced in recent years.

Introduction

A large number of epidemiological studies around the world, for instance EURODIAB and DIAMOND, suggest that there has been a significant and steady increase in the incidence of type 1 diabetes mellitus (T1DM) in the last two decades, especially in young children (1). The annual growth rate of incidence is almost constant, since it changed only slightly from 3.4% per annum in 1989-1998, to 3.3% per annum in 1999-2008 (2, 3). This trend has been recorded not only in the high-income European countries, which have the highest absolute incidence rate of T1DM (e.g. Finland 57.4/100 000; Sweden 36.6/100 000, slightly lower values are reported for Norway and Denmark and in the United Kingdom), but also in some middle-income European countries, such as Croatia (17.23 cases/100,000), Hungary (18.2 cases/100,000), Montenegro (18.6 cases 100,000) and Poland (16.5 cases/100 000) (4). Taking into account that, in relative terms, these latter countries are similar to Bosnia and Herzegovina culturally, genetically and economically, one should expect similar dynamics in our country.

The standardized incidence of T1DM for the 0-14 years age group in the Republika Srpska (a self-governing entity in Bosnia and Herzegovina) was estimated to be

8.2 cases /100 000 and the annual increase in the incidence was estimated to be 2.3% for the 1998-2010 period (5). These results allow the conclusion that the Republika Srpska may be placed within the group of European regions with a low incidence of T1DM. However, these estimates were based on estimates of census data in the Republika Srpska which proved to be largely incorrect. In addition, the results (6.9 cases/100,000 yearly) of a study conducted in the Tuzla Canton (in the north-eastern region of Bosnia and Herzegovina) provided further evidence to support the hypothesis that Bosnia and Herzegovina has a low incidence of T1DM (6). Taking into account the fact that these estimates were based on data collected in the relatively distant past and/or in a relatively small region, we decided to update the data and reach more reliable conclusions.

Thus, the aims of our study were to estimate the changes in the incidence trend for type 1 diabetes mellitus in children on the territory of Republika Srpska for the 2001-2016 period and to analyse the seasonal variations of disease diagnosis.

Methods

The Republika Srpska is a region in Bosnia and Herzegovina, located in south-east Europe, with an estimated total population of 1,171,179 in 2013 (based on the census conducted that year) (7). For the initial assessment we collected data using medical documentation from several hospital databases in the Republika Srpska. The secondary source of data collection was the health insurance fund of the Republika Srpska through which patients receive insulin and test stripes for glycaemia control. For the purposes of the study, we considered all new-onset physician-diagnosed T1DM individuals during the period from January 1, 2001 to December 31, 2016 in several health centres in the Republika Srpska. The EURODIAB criteria were used to assess eligibility for inclusion in the sample: physician's diagnosis of diabetes, children aged 0-14 years at diagnosis, residence in the Republika Srpska in the year of diagnosis, and daily insulin injections following diagnosis. The assessment was based on the capture-recapture method and was estimated to be 99%.

Statistical analysis

In order to evaluate the incidence rate, we needed to calculate the estimates of the total number of children 0-14 years old (disaggregated by gender and age in the categories 0-4, 5-9, 10-14 years) residing in the Republika Srpska in the 2001-2016 period. To this end, we used the results from the 2013 Bosnia and Herzegovina census (the first official census after 1991), and the estimates of the annual changes in total population provided by the Institute of Statistics of the Republika Srpska. Since we were not provided with estimates of the sizes of the relevant age and gender categories within this period, we calculated these by weighting the available census data with weights proportional to the estimated annual changes in the total population. Data from the patients were summarized as frequencies and percentages for categorical data, and measures of central tendency and variability for numeric data. A range of inferential techniques was used in later analyses: Poisson regression for estimating average incidence rates and respective confidence intervals, linear regression analysis to analyse trends through time, risk ratios for comparing the risks of different age groups, and the t-test and chi-square test for comparing gender differences. Analyses were performed using the R Project for Statistical Computing, version 3.3.3.

Results

In the time period between 2001 and 2016, a total of 294 children 0-14 years old were di-

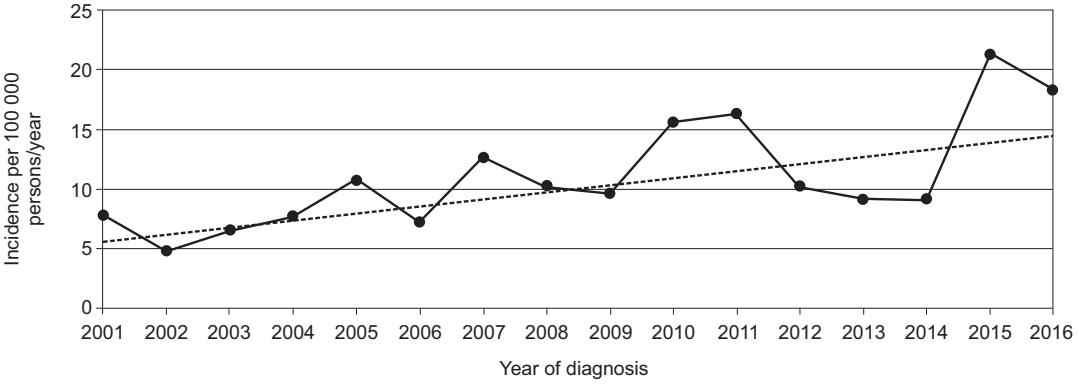

Fig. 1. *Incidence rates of type 1 diabetes mellitus per 100,000 persons per year, in the age group 0-14 years, 2001-2016. The dashed line shows the linear trend.*

Table 1. Incidence rates of type 1 diabetes mellitus according to sex-specific groups in the 2001-2016 period

Year	Type 1 patients			Incidence rate /100,000		
	Total	Male	Female	Total	Male	Female
2001	13	5	8	7.7	5.4	8.7
2002	8	4	4	4.7	4.3	4.4
2003	11	7	4	6.5	7.5	4.4
2004	13	7	6	7.7	7.5	6.5
2005	18	8	10	10.7	8.6	10.9
2006	12	5	7	7.2	5.4	7.6
2007	21	9	12	12.6	9.7	13.1
2008	17	4	13	10.2	4.3	14.2
2009	16	10	6	9.6	10.7	6.5
2010	26	10	16	15.6	10.7	17.5
2011	27	18	9	16.3	19.3	9.8
2012	17	9	8	10.2	9.7	8.7
2013	15	7	8	9.1	7.5	8.7
2014	15	8	7	9.1	8.6	7.6
2015	35	16	19	21.3	17.2	20.7
2016	30	21	9	18.3	22.6	9.8
Total	294	148	146	11.0	10.9	11.2

agnosed with T1DM, of which 148 (50.3%) were boys and 146 (49.7%) were girls. The average age for diagnosis was 8.4±3.6 years. The average incidence rate for the 2001 to 2016 period was 11.0 children/100,000, with the 95 percent confidence interval being bound by 9.8 and 12.4 children (calculations performed using Poisson distribution). As Fig. 1 shows, there was a notable year-to-year variation in incidence rates, however, a positive linear trend may be seen, which is statistically significant (r=0.71, P=0.002). Specifically, the average growth rate is 0.69 (95% CI: 0.30 to 1.08) children per year, which translates to an estimate of an average annual increase of 14.2% for the period from 2001 to 2016.

The minimum incidence rate was observed in 2002 with 4.7 diagnosed children per 100,000 of the population. Interestingly, incidence levels started to drop from 2011 (around 37% fall) and in 2014 declined to a level of 9.1 children/100,000; after that the incidence rate rapidly recovered and in 2015 reached an alarming peak of 21.3 children/100,000. The number of diagnosed cases more than doubled in 2015 when compared to 2014 (Table 1).

Gender as a correlate of incidence trends

Gender was not shown to be an important correlate of incidence in the overall sample. Boys and girls were equally likely to be diagnosed with T1DM. The average incidence for boys was 10.8, while for girls it was 11.2. The relative risk ratio was practically equal to one, and logically, it was not statistically significant (RR=1.00, 95% CI: 0.89 to 1.12, z=0.02, P=0.985). Furthermore, we did not find gender differences either in the age of children when diagnosed (t=0.21, P=0.831) or in changes in the gender proportion in diagnoses through the years (χ^2=18.0, P=0.265).

Age as a correlate of incidence trends

We separated the sample of patients into three different age groups: the first group from 0 to 4 years, the second group composed of children aged from 5 to 9 years, and the third group with children from 10 to 14 years. The smallest number of patients belonged to the 0 to 4 years age group with 17.0% of all cases (n=50), in the age group from 5 to 9 years there were 39.8% (n=117), while there were 43.2% (n=127) patients diagnosed at the ages of 10 to 14 years. Accordingly, the incidence rate at the age from 0 to 4 years was 5.8 children/100,000, for the 5-9 years

Table 2. Incidence rates of type 1 diabetes mellitus according to 0-14 years age groups, in the Republika Srpska, 2001-2016

Year	Type 1 patients			Incidence rate /100,000		
	0-4 yr	5-9 yr	10-14 yr	0-4 yr	5-9 yr	10-14 yr
2001	1	9	3	1.8	16.3	5.1
2002	3	1	4	5.5	1.8	6.8
2003	3	7	1	5.5	12.7	1.7
2004	1	2	10	1.8	3.6	17.0
2005	3	7	8	5.5	12.8	13.6
2006	0	5	7	0.0	9.1	11.9
2007	1	9	11	1.8	16.5	18.8
2008	1	9	7	1.9	16.5	12.0
2009	6	6	4	11.1	11.0	6.9
2010	9	10	7	16.7	18.4	12.0
2011	4	13	10	7.4	24.0	17.2
2012	3	7	7	5.6	12.9	12.0
2013	4	3	8	7.5	5.6	13.8
2014	4	6	5	7.5	11.1	8.6
2015	4	11	20	7.5	20.5	34.7
2016	3	12	15	5.7	22.5	26.2
Total	50	117	127	5.8	13.5	13.6

group 13.5/100,000, and for the 10-14 years group 13.6/100,000. In comparison to the youngest group, the estimated risk in the 5 to 9 years group was 2.32 times higher (95% CI: 1.68 to 3.30, P<0.001), while the risk in the 10 to 14 years group was 2.34 times higher (95% CI: 1.71 to 3.34, P<0.001). When comparing the second and third groups, the estimated risk was about the same (RR=1.01, 95% CI: 0.79 to 1.30, P=0.949).

When it comes to the incidence trends through time, we detected a linear trend in all three age groups. This increase was most evident for the oldest group, where the annual rate of increase was 1.05 children per year (95% CI: 0.28 to 1.83; r=0.62; P=0.011). The rate of increase of incidence is clearly visible in the other two age categories, but it is slightly lower and, due to small sample sizes, it did not reach the level of statistical significance (e.g. data for a total of 16 years, meaning n=16). For the second sample group, children aged between 5 and 9 years, the increase in T1DM diagnosis was 0.61 children per year (95% CI: −0.09 to 1.30; r=0.45, P=0.081), while for the ages of 0-4 years the average annual increase in incidence was 0.37 (95% CI: −0.08 to 0.82; r=0.42, P=0.102; Table 2).

Seasonality of incidence rates

Finally, we tested whether there was an association between calendar months and the frequency of diagnosis of T1DM. Indeed, Fig. 2 illustrates that noticeable peaks of T1DM incidence were observed in January and February, while in May, June and July T1DM was diagnosed less frequently than in other months.

Discussion

In this study we explored the incidence rates for children diagnosed with diabetes mellitus type 1 aged 0-14 years in the Republika Srpska in the 2001-2016 period. Unfortunately, our findings support the hypothesis that incidence levels are on the rise. Specifically, we found the average incidence levels for the 2001-2016 period to be 11.0 cases/100,000 compared to the previous estimates for the 1998-2010 period at 8.2 cases/100, 000. We found that the annual incidence rate increase

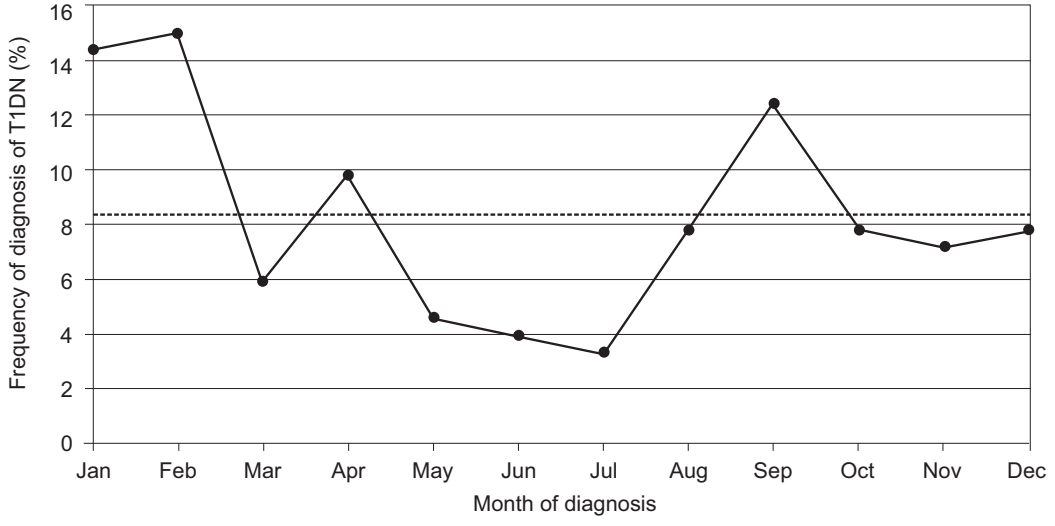

Fig. 2. *Incidence of type 1 diabetes mellitus in the Republika Srpska (2001-2016) by calendar months. The dashed line denotes the expected average incidence rate.*

was equal to 14.2%, meaning that, on average, the rising trend was noticeably higher compared to the annual increase of 2.3% estimated for the 1998–2010 period. In fact, this difference is partly due to the fact that the total population of Bosnia and Herzegovina and the Republika Srpska was overestimated in a former study, but nevertheless our results show that in recent years the Republika Srpska shifted from a low-incidence to a moderate-incidence region/country, according to the WHO classification (8).

Moreover, our results showed that children older than 4 years were more likely to be diagnosed with T1DM, which is similar to the results published in studies in Croatia and Norway (9, 10). On the other hand, our results differ from the results recorded in Montenegro, where the incidence is estimated to be significantly higher (17 cases/100,000), and where the incidence is estimated to be more frequent in younger male children, aged up to 4 years. (11) In contrast, in our study boys and girls were equally likely to be diagnosed with T1DM. Furthermore, in Croatia the incidence escalated to 17.23 cases / 100 000 for the 2004 to 2012 period, with the highest incidence rate of 20.0 cases/100,000 for the 10-14 years age group. Comparable results were found in Norway, where for the 2004-2012 time period the incidence rate reached a level of 32.7/100,000 and the most significant incidence was experienced in the 10-14 age group for both genders. Similarly, a relatively high incidence rate of 37.6 cases/100,000 was obtained in Sweden for the 10-14 years age group, however in all previous years the higher incidence rate was characteristic of young children (12).

In our country, there was a relatively small increase in incidence for children with T1DM aged 0-4 years, compared to other European states, which may be explained by good prophylaxis using 400 IU of vitamin D doses in the first year of life, and during the winter months between the ages of 2 and 3 years. Also, an additional explanatory factor for our results might be the fact that our country's climate is continental, meaning that we have sufficient sunny days, which also might contribute to the levels of vitamin D (13, 14).

There are several possible explanations for the increase observed in our region. The Western lifestyle (particularly fast food eating habits) has become common practice in the last 16 years for children in the Republika Srpska, which may be considered as one of the possible factors contributing to the increase in the number of patients. In addition, the months with the most frequent diagnosis of T1DM were January and February (and the ones with least diagnoses were May, June, and July), which could be closely connected to the fact that respiratory infections are common during these months and that there is a lack of exposure to sunlight which – a lower D vitamin intake - could further contribute to the incidence of T1DM. (15)

Conclusion

Our results are in line with the trend of increasing T1DM incidence rate in Europe, which is particularly characteristic for eastern European countries. That said, our results show differences when it comes to age groups with the highest increase of incidence; namely, we observed the highest increase in diagnosis in children aged from 10 to 14 years compared to other European countries reporting the largest incidence for younger children. Additionally, we found that the incidence trend was indeed linear, but with many year-to-year variations, which might be due to external factors. The final average incidence rate (11.0/100, 000) positions our region among European countries with moderate T1DM incidence rates (16). Taking into account the fact that we performed

our study on approximately 20 patients per year, we may say that the size of our sample is a rather limiting factor. Overall, our study creates a solid basis for local health policy makers to improve awareness of the increasing incidence rates, and to undertake more structured prevention as part of secondary and tertiary prevention programs.

Authors' contributions: Conception and design: GBR, VM, OLJ and SL; Acquisition, analysis and interpretation of data: GBR, VM, OLJ and SL; Drafting the article: GBR, VM, OLJ and SL; Revising the article critically for intellectual content: GBR and SL; Approved final version of the manuscript: GBR, VM, OLJ and SL.

Conflict of interest: The authors declare that they have no conflict of interest.

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