

# Rising incidence of childhood type 1 diabetes in Montenegro

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**Introduction** The incidence rate of childhood type 1 diabetes continues to rise across Europe by an average of approximately 3–4% per annum.

**Objective** The aim of this study was to examine incidence and trends of type 1 diabetes in children aged 0–14 years in Montenegro from 1997 to 2011.

**Methods** This was a prospective study. Primary case ascertainment was from a diabetes register, and a secondary independent data source was from hospital notifications. Case ascertainment was 100% complete using the capture-recapture method. Standardized incidence rates were calculated and trends estimated using the Poisson regression.

**Results** A total of 298 children (157 boys and 141 girls) were diagnosed with type 1 diabetes before 15 years of age during 1997–2011. The mean age-standardized incidence was 15.0/100,000 persons (95% CI: 12.3–17.6) during this period, increasing from 11.7/100,000 in 1997 to 18.8/100,000 in 2011. The age-specific rates per 100,000 persons per year were 10.7, 17.2, and 18.2 at ages 0–4 years, 5–9 years, and 10–14 years, respectively. A significant linear trend in incidence ( $p = 0.002$ ) has been observed over time, with an average annual increase of 4.2%. The increase in incidence was present in both genders, with the largest relative increase in the 0–4 years age group for boys (11.0%;  $p = 0.006$ ).

**Conclusion** The incidence of type 1 diabetes in Montenegro children continues to increase. We need further monitoring and additional research in order to explain the cause.

**Keywords:** type 1 diabetes, incidence; type 1 diabetes, children; Montenegro

## INTRODUCTION

The prevalence of type 1 diabetes (T1D) varies greatly between countries. The lowest incidence (<1/100,000 persons per year) was reported in the populations from China and South America, and the highest incidence (>20/100,000 per year) was reported in Sardinia, Finland, Sweden, Norway, Portugal, the United Kingdom, Canada, and New Zealand [1]. The incidence rate of childhood T1D continues to rise across Europe by an average of approximately 3–4% per annum. Recent incidence rate trends in childhood T1D have been described in publications by the EURODIAB [2], DIAMOND Project [3], and the SEARCH for Diabetes in Youth (SEARCH) study [4].

While some studies in Europe have found that the greatest increase trend in the incidence of T1D occurred in children under five years of age [5], others showed that the trend of T1D in this age group increased to a certain point of time after which it remained stable [6]. The increased trend in T1D incidence and wide variations in the incidence could be explained by the change of environmental factors as well as of lifestyle, and their influence on persons with suitable genetic predisposition [2].

In the Balkan and Mediterranean countries, the incidence rates of T1D also show wide differences, whereas for some of them, there are still no relevant data [7].

The incidence of childhood-onset T1D mellitus among Montenegro children under 15 years of age during 1996–2006 was 13.4/100,000 per year. The annual increase rate for this period was 4.6% [8].

## OBJECTIVE

This study aimed to update the previous 10-year research on the incidence and trends of type 1 diabetes in 0–14-year-old children in Montenegro.

## METHODS

### Geographical and population data

Montenegro is located in South-Eastern Europe, with an area of 13,812 km<sup>2</sup> and a population of 620,145 (according to the census of 2011), including 118,751 children (19%) in the 0–14 years group. The climate is continental, Mediterranean and mountainous. Montenegro is a country with slow but sustainable economic growth. Gross domestic product per capita in 2000 was €1,750, whereas in 2011 it was €5,211. The infant mortality rate in 2000 was 11.7; in 2011 it was 5.1 per 1,000 live births [9].

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## Data collection

Diabetes onset in children and adolescents aged <15 years was documented according to the EURODIAB criteria [2]. All Montenegro children with newly diagnosed T1D were admitted to the University Children's Hospital in Podgorica, where they have been further monitored in the children's endocrinology outpatient clinic.

Children with newly diagnosed T1D in Montenegro who were listed on the National Public Health Institute diabetes register and Hospital Discharge Register in 1997–2011 were included in a cohort study. Data collected for each case for the diabetes register include name, date of birth, sex, place of residence, and date of diagnosis taken as the date of first insulin administration. Completeness of ascertainment was estimated with the capture–recapture method [10].

## Population data

Children population was obtained from 2003 and 2011 census data, as well as the mid-year population estimates for other years in the study, which have been published by the Statistical Office of Montenegro [9].

## Statistical analysis

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 0–14 age group (0–4, 5–9, and 10–14 years) for each sex. Age and sex standardized incidence rates were obtained for the 0–14 years age group using the direct method with a world standard population. Poisson regression models were used to analyze the changes in incidence of T1D mellitus for 1997–2011 period and to examine the incidence differences among the age groups, and between girls and boys, as well as to estimate the temporal trend in incidence. P-value of less than 0.05 was

considered statistically significant. Statistical analyses were performed using SPSS 17 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Incidence

In the period from 1997 to 2011, 298 children (157 boys and 141 girls) were diagnosed with T1D mellitus. Seven of them were found by primary source only, and 291 (97.7%) were identified by both sources providing 100% ascertainment. The largest number of patients was recorded in the 10–14 age group – 129 (43.3%) – while the smallest number was recorded in the 0–4 age group – 65 (21.8%).

The mean age and sex standardised incidence rate over the 15-year period was 15.0/100,000/year (95% CI: 12.3–17.6). The incidence rate ranged from 11.7/100,000/year (95% CI: 6.2–17.1) at the beginning of the study in 1997 to 18.8/100,000/year (95% CI: 11.1–26.6) at the end of the study in 2011. The peak annual incidence rate occurred in 2007 (21.8/100,000/year).

### Age group

The mean incidence was 10.7 (95% CI: 7.3–14.0) for the 0–4 age group, 17.5 (95% CI: 13.1–21.9) for 5–9 age group, and 17.9 (95% CI: 14.7–21.0) per 100,000 children/year for 10–14 age group (Table 1). Differences between the groups were statistically significant ( $p = 0.001$ ). The peak annual incidence rate occurred in 2007 in 5–9 age group – 21.8/100,000/year (95% CI: 13.7–30.0), more precisely in 5–9-year-old boys – 25.3/100,000/year (95% CI: 13.2–37.5).

### Sex

The mean age standardised incidence rate for the 15-year study period was 15.4 per 100,000/year (95% CI: 11.6–19.1)

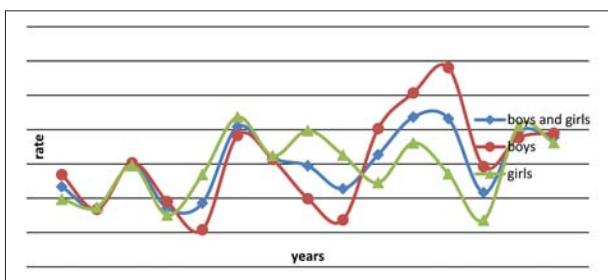
**Table 1.** Mean age- and sex-specific incidence rates of type 1 diabetes mellitus in Montenegro during 1997–2011 and percentage increase incidence per year

Sex	Age groups	Population	Number of cases	Annual increases of incidence % (95% CI)	p-value	Mean incidence rate (95% CI)
Boys	0–4	21,437	35	11.0 (3.2–18.9)	<b>0.006</b>	11.9 (6.2–17.6)
	5–9	22,184	49	7.7 (3.4–14.3)	<b>0.021</b>	15.1 (9.0–21.2)
	10–14	23,843	74	1.9 (-3.4–7.1)	0.487	20.9 (15.8–25.9)
	0–14*	67,464	158	5.2 (1.5–8.8)	<b>0.005</b>	15.4 (11.6–19.1)
Girls	0–4	19,772	30	0.0 (-8.2–8.3)	0.994	10.1 (7.5–12.8)
	5–9	20,647	61	6.3 (0.5–12.2)	<b>0.035</b>	20.1 (14.1–26.0)
	10–14	22,380	49	0.8 (-5.6–7.3)	0.801	14.7 (11.4–17.9)
	0–14*	62,800	140	3.0 (-0.8–6.8)	0.123	14.5 (11.9–17.1)
All	0–4	41,209	65	4.8 (-0.8–10.4)	0.096	10.7 (7.3–14.0)
	5–9	42,832	110	7.0 (2.6–11.3)	<b>0.002</b>	17.5 (13.1–21.9)
	10–14	46,223	123	1.5 (-2.6–5.6)	0.479	17.9 (14.7–21.0)
	0–14**	130,264	298	4.2 (1.5–6.8)	<b>0.002</b>	15.0 (12.3–17.6)

\* age- and sex-standardized incidence rate

\*\* age-standardized rate

CI – confidence interval



**Graph 1.** Mean age-specific incidence of type 1 diabetes in Montenegro boys and girls, 0–14 years old (1997–2011)

in boys and 14.5 (95% CI: 11.9–17.2) in girls. There was no significant difference between incidence in boys and girls ( $p = 0.671$ ) (Graph 1).

## Incidence trends

The incidence has increased by an average of 4.2% per year (95% CI: 1.5–6.8;  $p = 0.002$ ), in boys 5.2% per year (95% CI: 1.5–8.8;  $p = 0.005$ ), in girls 3% per year (95% CI: -0.8–6.8;  $p = 0.123$ ) (Graph 2).

The highest annual increase of 11% (95% CI: 3.2–18.9;  $p = 0.006$ ) was recorded in 0–4-year-old boys, but the lowest was in 0–4-year-old girls – 0% (95% CI: -0.8–6.8;  $p = 0.123$ ).

## DISCUSSION

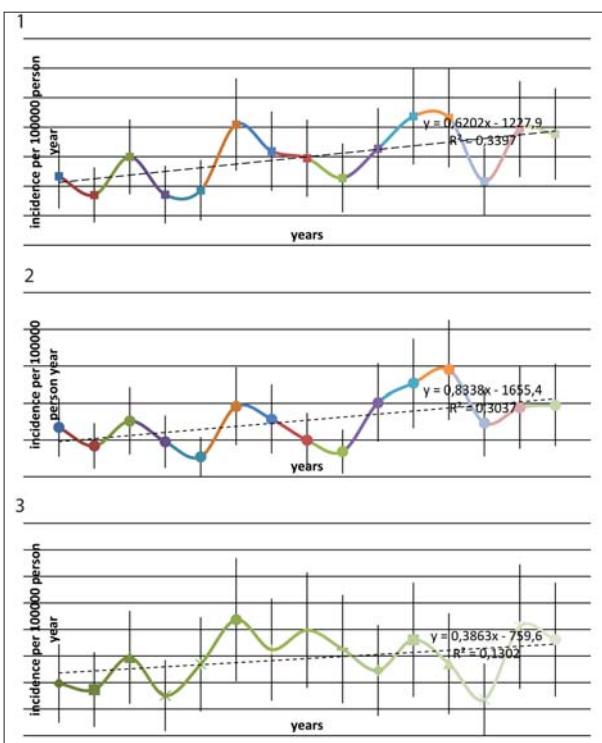
The mean age- and sex-standardized incidence rate of T1D in Montenegro for the study period of 1997–2011 was 15.0/100,000/year. The previous study performed in 2009 had shown T1D incidence of 13.4/100,000/year [8]. Montenegro belongs to the group of countries with high risk for development of T1D [3]. This rate is close to the rates in some European countries such as Austria [11], Hungary [12], Luxembourg [2], some parts of Poland [13], and Belgium [14].

The frequency of T1D is rising in almost every population. The prevalence estimates show that there are about 500,000 children under the age of 15 with T1D worldwide [15].

Most studies report an increase in incidence with increasing age, with the highest incidence occurring in the 10–14-year-old age group [3, 16]. We also found the highest incidence in this age group during the whole study period: 18.2 (95% CI: 14.9–21.4).

In this study there was no difference in the incidence between the sexes. Some studies have also shown no difference in the incidence of T1D mellitus between boys and girls [17, 18], but some countries show a female preponderance [19]. A significant male excess was found in Italy and Spain [20, 21], as well as in countries/regions with the highest incidence of T1D, such as Sardinia [22].

The increase in incidence of T1D in Montenegro is statistically significant, with a yearly average increase of 4.2% ( $p = 0.002$ ). In boys, the yearly average increase was



**Graph 2.** Trends in sex-specific annual incidence (95% confidence interval) of type 1 diabetes mellitus in 0–14-year-olds in Montenegro from 1997 to 2011; observed rates in boys and girls (1), boys (2), and girls (3).

5.2% ( $p = 0.005$ ), but in girls the yearly average increase of incidence was not statistically significant – 3% ( $p = 0.123$ ). The increase in incidence trend in Montenegro is approximately equal to the yearly increase in incidence of T1D in Slovenia [2].

Publications by the EURODIAB registries in Europe showed acceleration in the incidence trend in: Austria, Germany (Baden-Württemberg), Hungary, and Lithuania, and deceleration in the rate of increase in the Czech Republic, Poland (Katowice), UK (Oxford and Yorkshire), and Germany (Düsseldorf/North Rhine-Westphalia) in 1999–2008 [2].

Our findings suggest that the largest annual increase incidence is seen in boys less than five years of age, which is consistent with previously published data [23, 24], some of which assume that male sex is a risk factor for early manifestation of the disease [17].

The incidence rate of T1DM in children (age range 0–14 years) varies widely in Mediterranean and neighboring countries/regions [7], ranging from 5.8/100,000/year in the Former Yugoslav Republic of Macedonia [2], to 44.8/100,000/year in Sardinia [22].

There are great variations in incidence rates across Europe and even within various regions in an individual country. This demonstrates the interplay between genes and environment [3, 16].

There are also differences in the incidence of T1D in the seven states of the former Yugoslavia. In comparison to other former Yugoslav countries, Montenegro has the highest T1D mellitus incidence. The standardized incidence (depending on the follow-up period) of T1D (age

group 0–14 years) in Serbia was 10.4–15.5/100,000 [24, 25], in Croatia 8.2–17.23/100,000 [2, 26], in Slovenia 11.1–14.6/100,000 [2], Bosnia and Herzegovina (Republic of Srpska) 7.5/100,000 [27], Bosnia and Herzegovina (Tuzla Canton) 7.1/100,000 [28], Former Yugoslav Republic of Macedonia 5.6–5.8/100,000 children per year [2].

The incidence of T1D mellitus in Montenegro increased continuously during the 15-year survey. The raise of incidence per year was noticed in all age groups except in 0–4-year-old girls. We have no reasonable explanation for this. Recent studies demonstrate that many of the environmental triggers are associated with T1D [29]. According to some authors, breastfeeding, nicotinamide, zinc, and vitamins C, D, and E have been reported to possibly have a protective effect against T1D, whereas N-nitroso compounds, cow milk, increased linear growth, and obesity may increase the risk [30].

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During the last 15 years, the country has undergone significant changes as a result of wars in the region, isolation, economic crisis, and the abrupt transition to the western lifestyle. Recent studies in Montenegro show that significant changes occurred in people's diet and that there is more frequent occurrence of obesity among schoolchildren [31]. We also have the migration of population from villages to towns. Therefore, further genetic, immunologic, and ecologic researches are required to explain the rapid growth of the T1DM incidence in Montenegro.

## CONCLUSION

The incidence of T1D in Montenegro children continues to increase. We need further monitoring and additional research in order to explain the cause.

- diagnosed in 1990-1997: a significant increase in incidence and male predominance in the age group 0-4 years. Collaborators of the Czech Childhood Diabetes Registry. Diabet Med. 2000; 17(1):64-9. [DOI: 10.1046/j.1464-5491.2000.00202.x] [PMID: 10691162]
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## Раст инциденце дијабетеса типа 1 код деце у Црној Гори

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### КРАТАК САДРЖАЈ

**Увод** Годишњи пораст инциденце дијабетес мелитуса типа 1 у Европи креће се од 3% до 4%.

**Циљ рада** Циљ студије је утврдити инциденцу и тренд инциденце дијабетес мелитуса типа 1 код деце узраста 0-14 година у Црној Гори за период од 1997 до 2011.

**Методе рада** Спроведена је проспективна студија. Као први извор послужили су подаци о новооболелим пацијентима из Регистра за дијабетес, а као други извор коришћена су отпушна писма деце са новооткривеним дијабетесом типа 1. Поузданост података испитана је *capture-recapture* методом. За рачунање стандардизоване инциденце коришћена је метода директне стандардизације на стандардну светску популацију за узраст 0-14 година. За анализу промена у инциденци за период од 1997. до 2011. примењиван је *Poisson log* линеарни регресиони модел.

**Резултати** У испитиваном периоду регистровано је 298 деце оболеле од дијабетес мелитуса типа 1 (157 дечака и 141 девојчица). Стандардизована инциденца за целу старосну групу била је 15,0/100.000 по години (95% CI: 12,3-17,6) и повећавала се од 11,7/100.000 (1997. год.) до 18,8/100.000 (2011. год.). Инциденца према старосним групама кретала се од 10,7/100.000 у узрасту 0-4 године, 17,2/100.000 у узрасту 5-9 година до 18,2/100.000 и узрасту 10-14 година. Забележен је статистички значајан узлазни тренд инциденце ( $p = 0,002$ ) са годишњим порастом од 4,2%. Повећање инциденце је присутно код оба пола са највећим годишњим порастом код дечака узрасту 0-4 године (11,0%;  $p = 0,006$ ).

**Закључак** Инциденца дијабетеса типа 1 у Црној Гори и даље расте. Потребни су даље праћење и допунска испитивања да би се разјаснило узрок.

**Кључне речи:** Црна Гора; дијабетес типа 1, инциденца; дијабетес типа 1, деца

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