Incidence of Type 1 Diabetes Mellitus in 0 to 14-yr-old Children in Croatia – 2004 to 2012 Study

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Original Article

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Rojnic Putarek N, Ille J, Spehar Uroic A, Skrabic V, Stipancic G, Krnic N, Radica A, Marjanac I, Severinski S, Svigir A, Bogdanic A, Dumic M. Incidence of type 1 diabetes mellitus in 0 to 14-yr-old children in Croatia – 2004 to 2012 study.
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Background: The incidence of type 1 diabetes mellitus (T1DM) among children and adolescents increased during the last 50 yr. The T1DM incidence in Croatia was 8.87/100.000/yr over 1995–2003, with an annual increase of 9%, which placed Croatia among countries with moderate risk for T1DM.
Aim: To investigate incidence rates and trends of T1DM from 2004 to 2012 in 0 to 14-yr-old Croatian children, and to compare the results with previous studies in Croatia and other European countries.
Methods: T1DM crude incidence rates are estimated for the entire group and three subgroups: 0–4, 5–9, and 10–14 yr. Standardized incidence is calculated using the method of direct standardization according to World Health Organization (WHO) standard world population. The incidence rates by gender, age groups, seasonality, and calendar year, and their interactions were analyzed using Poisson regression model.
Results: A total of 1066 cases were ascertained over 2004–2012. The standardized incidence was 17.23/100.000/yr (95% CI: 16.19–18.26), with no significant differences in incidence rates or trends between boys and girls. Statistically significant annual increase of 5.87% ($p < 0.001$) was found for the whole group, and for the subgroups 5–9 yr (6.82%; $p < 0.001$) and 10–14 yr (7.47%; $p < 0.001$). In the youngest subgroup (0–4 yr), annual increase was lower (2.43%; $p = 0338$) and not statistically significant.
Conclusion: The incidence of childhood T1DM is increasing in Croatia, thus placing Croatia among countries with high risk for T1DM. The annual increment of 5.87% is considerably lower than 9.0% reported earlier, but still higher than the European average (3.9%). The increase in incidence ceased in youngest children.

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Key words: children and adolescents – Croatia – incidence variation – type 1 diabetes mellitus

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The incidence of type 1 diabetes mellitus (T1DM) among children and adolescents has increased markedly in the course of the last five decades and concurrently the mean age at diagnosis has decreased. T1DM incidence is on the rise worldwide (1–3), in particular in children younger than 5 yr (1, 2, 4–8). These trends point to a critical role of exogenous factors responsible for T1DM as genetic factors alone cannot

explain this rapid increase (9). Epidemiological studies carried out throughout the world have demonstrated variable incidence of T1DM between and within countries (1, 10–12) ranging from 0.1/100.000/yr in China and Venezuela (11, 12) to 37.8/100.000/yr in Sardinia and more than 64/100.000/yr in Finland (13, 14).

The incidence of T1DM in children and adolescents 0–14 yr in Croatia for the period 1995–2003 was found to be 8.87/100.000/yr, which placed Croatia in a group of countries with moderate risk for development of T1DM according to World Health Organization (WHO) (15). During the study period, the incidence increased significantly with an average annual trend of 9% (16). This was considerably greater than data for other European and worldwide populations with the average annual increase of 5.3% in North America, 4.0% in Asia, and 3–4% in Europe, while in Central America and the West Indies the trend decreased by 3.6% (13, 17, 18). These data stress the necessity for evaluation of the incidence of childhood diabetes in more diverse populations throughout the world in order to contribute to better understanding of the T1DM etiopathogenesis.

The aim of this study was to determine incidence rates of T1DM in children 0–14 yr in Croatia for the period 2004–2012, to compare the incidence rates with previous data for 1995–2003, and to compare the results with similar studies conducted in other countries in the same period.

Patients and methods

The population data were obtained from Central Bureau of Statistics of the Republic of Croatia (19). The number of children younger than 15 yr in Croatia for studied period varied from 699.400 in 2004 to 640.088 in 2012. Croatia is a middle European country located at the Adriatic Sea, with a population of 4.284.889 people according to the 2011 population census (19).

Children aged 0–14 were diagnosed with T1DM according to the WHO criteria (20) and patients with diabetes secondary to other causes were excluded. The study included patients diagnosed with T1DM from 1 January 2004 to 31 December 2012. The date of diagnosis was defined as the date when insulin therapy was initiated. The number of newly diagnosed patients with T1DM was obtained from the registry collecting data from 19 pediatric departments distributed across the country, thus covering entire Croatian territory. Uniformity of diabetes registration was provided by collecting the data of newly diagnosed patients through standardized questionnaire following the end of each calendar year. The data were collected from the primary sources by a single person, and are compiled through Central diabetic register situated in our Center. Data included full name, date of birth, gender, date of first insulin administration and address. All patients were residents of Croatia.

Completeness of ascertainment was verified using the alternative source of patients recruited from the membership list of 'Adults for children with diabetes', an independent, humanitarian diabetes association, established in 1997, which brought together more than 600 families of children with diabetes since its founding. Members in whom insulin therapy was introduced by the age of 15, and who were registered in the association from 2004 to 2012 were included in the study. The capture–recapture method was used to estimate completeness of ascertainment.

Statistical analysis

T1DM crude incidence rates were estimated as a number of newly diagnosed patients per 100.000/yr for all children aged 0–14 yr, separately between three age subgroups: 0–4, 5–9, and 10–14 yr, and also according to gender. The 95% confidence intervals were estimated by Wald's method using normal approximation of Poisson distribution. The method of direct standardization to WHO standard world population younger than 14 yr was used for calculation of standardized incidence in the whole group and separately according to gender. Poisson regression model was used to analyze the incidence rates by gender, age groups, seasonality, and calendar year.

Results

During the study period 2004–2012, a total of 1066 children (529 girls and 537 boys) aged 0–14 were diagnosed with T1DM in Croatia. The completeness of ascertainment for the whole period was estimated to be 96,69%, i.e., out of 1066 newly diagnosed patients, 1054 were ascertained through primary source of hospital reports, 12 through the secondary source, the membership list of 'Adults for children with diabetes' association and 352 through both sources. The crude incidence for the whole period was 17.44/100.000/yr (95% CI: 16.39–18.49, range: 12.89–23.43). Standardized incidence for the same period was 17.23/100.000/yr (95% CI: 16.19–18.26; Table 1).

Gender

The crude incidence rate in boys was 17.18 per 100.000/yr (95% CI: 15.73–18.64, range: 11.19–23.75) and in girls 17.71/100.000/yr (95% CI: 16.2–19.22, range: 12.58–23.10; Table 1). Standardized incidence for the same period was 16.91/100.0000/yr (95% CI: 15.48–18.35) in boys and 17.55/100.0000/yr (95% CI: 16.05–19.05) in girls. Female to male incidence ratio was 1.02. Using Poisson regression method the risk for

Table 1. Type 1 diabetes mellitus (T1DM) incidence rates per 100.000 children per year according to age groups and sex for the period of 2004–2012*

Age groups (yr)	Sex	T1DM patients (n)	Population (n)	Incidence rate/100.000 (95% CI)
0–4	Boys	125	967.106	12.93 (10.66–15.19)
	Girls	122	920.065	13.26 (10.91–15.61)
	All	247	1.887.171	13.09 (11.46–14.72)
5–9	Boys	170	1.022.097	16.63 (14.13–19.13)
	Girls	203	977.176	20.77 (17.92–23.63)
	All	373	1.999.273	18.66 (16.76–20.55)
10–14	Boys	242	1.135.785	21.31 (18.62–23.99)
	Girls	204	1.089.587	18.72 (16.15–21.29)
	All	446	2.225.372	20.04 (18.18–21.90)
0–14	Boys	537	3.124.988	17.18 (15.73–18.64)
	Girls	529	2.986.828	17.71 (16.05–19.22)
	All	1066	6.111.816	17.44 (16.39–18.49)
Standardized incidence	Boys			16.91 (15.48–18.35)
	Girls			17.55(16.05–19.05)
	All			17.23(16.19–18.26)

*Data are presented as number of patients and population in each age subgroup and entire group, crude and standardized incidence rates including confidence interval for boys, girls, and entire group.

T1DM in boys was estimated to be 0.97 times (95% CI: 0.86–1.094) lower than in girls. No statistically significant difference ($\chi^2 = 0.243$; $p = 0.622$) was found in the T1DM incidence rates between boys and girls in the whole group. In the 5–9 yr subgroup significantly more girls were diagnosed with T1DM ($p = 0.032$). The risk for T1DM in this age group was 1.249 times (95% CI: 1.019–1.531) higher in girls than in boys. In the other two age subgroups no significant difference in the incidence of T1DM over this period was found between sexes.

Age groups

The mean age at diagnosis was 8.53 yr (range: 0.33–14.97 yr) for the entire group, 8.37 yr (range: 0.46–14.93 yr) for the girls, and 8.68 yr (range: 0.33–14.97 yr) for the boys.

The differences in T1DM incidence rates among all age subgroups were statistically significant ($\chi^2 = 30.427$; $p < 0.001$). The highest incidence was observed in the 10–14 yr subgroup, i.e., 20.04/100.000/yr (95% CI: 18.18–21.90), followed by 5 to 9-yr-old subgroup, i.e., 18.66/100.000/yr (95% CI: 16.76–20.55), and the least in the 0–4 yr subgroup, i.e., 13.09/100.000/yr (95% CI: 11.46–14.72); Table 1; Fig. 1).

The estimated risk for T1DM in children aged 5–9 was 1.425 times higher (95% CI: 1.214–1.674) and in children aged 10–14 1.531 times higher (95% CI: 1.214–1.674) than in children aged 0–4. There was no significant difference in the incidence rates between the age subgroups according to the gender.

Seasonality

A significant difference was found in T1DM incidence according to seasonality ($p = 0.001$). Higher incidences for the entire group were observed in the autumn and winter, i.e., 302 (28.2%) and 290 (27.2%), respectively as compared to spring and summer with 216 (20.26%) and 258 (24.2%) children, respectively.

Incidence rate trends

Statistically significant increase in incidence was found for the entire group ($\chi^2 = 22.605$, $p < 0.001$) in the observed period, with an annual increase in incidence of 5.87% (95% CI: 3.36–8.33).

The annual increment of incidence rate was statistically significant in 5–9 yr subgroup [6.82% (95 CI: 2.74–11.07) $p < 0.001$] and in 10–14 yr subgroup (7.47%; 95 CI: −3.67 to 11.52), but not in the 0–4 yr subgroup (2.43%, 95% CI: −2.47 to 7.47; Table 2, Fig. 1). No statistically significant difference in incidence rate was observed between boys and girls.

Discussion

The incidence of T1DM in Croatian children aged 0–14 for the period 2004–2012 is still increasing (Fig. 1). The estimated incidence for the whole age group has doubled compared to the previous period 1995–2003 (17.44/100.000/yr in 2004–2012 vs. 8.87/100.000/yr in 1995–2003) (16). Currently, this places Croatia in the group of countries with high risk for childhood T1DM according to WHO (15).

Wide range in T1DM incidence rates (from 5.8/100.000/yr in Macedonia to 36.6/100.000/yr in Sweden) during the period of 2004–2008 have been found in the European countries (20), and some of them have T1DM incidence rates similar to Croatian (Austria 17.5/100.000/yr, Belgium 15.9/100.000/yr, Hungary 18.3/100.000/yr, Luxemburg

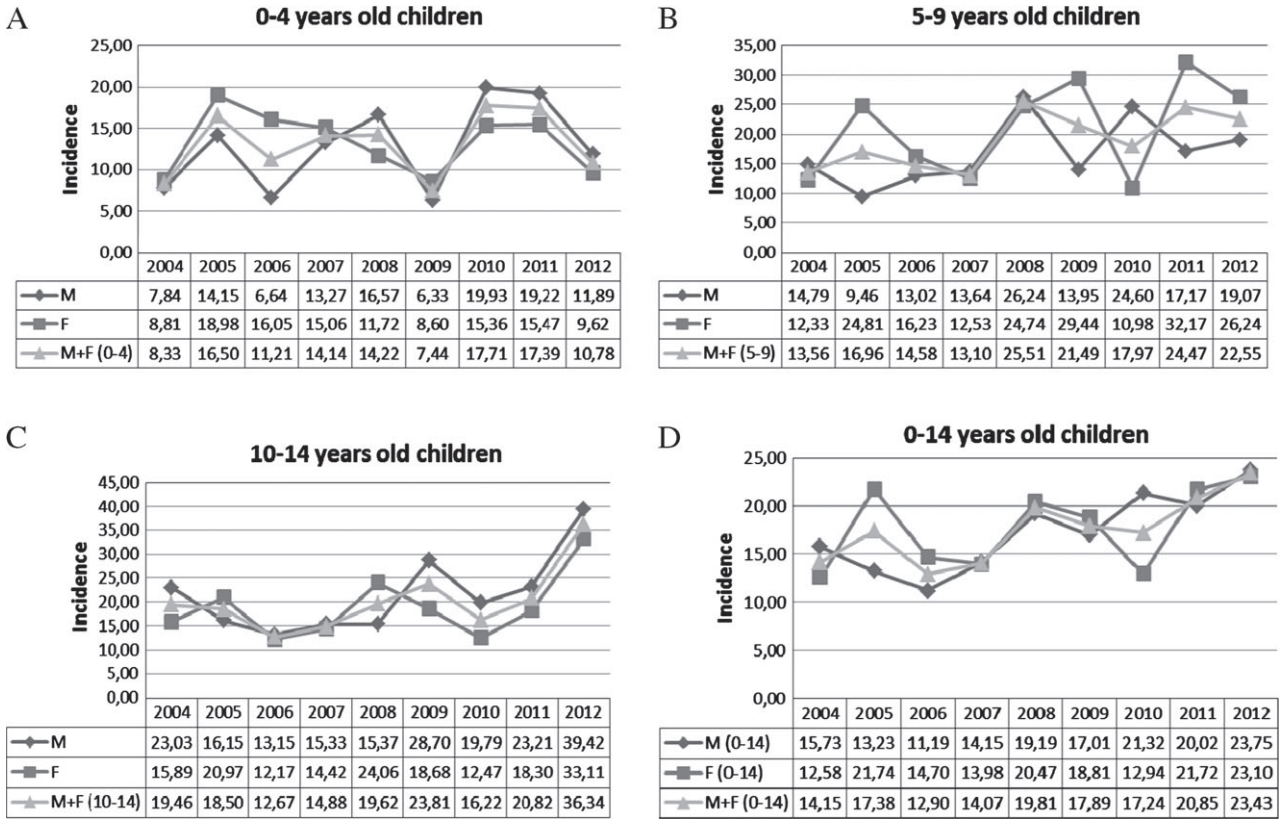

Fig. 1. Incidence rates of type 1 diabetes mellitus (T1DM) per 100.000 person per year according to age groups and year of diagnosis. *Data are presented as crude incidence rates in (**A**) 0–4 yr old subgroup, (**B**) 5–9 yr old subgroup, (**C**) 10–14 yr old subgroup, and (**D**) entire group.

Table 2. Incidence rates and trends of type 1 diabetes mellitus (T1DM) according to sex and age groups

Age groups (yr)	Sex	Average annual change of incidence	95% CI		p
			Lower	Upper	
0–4	M + F	2.43%	−2.47%	7.47%	0.338
5–9	M + F	*6.82%*	2.74%	11.07%	*<0.001*
10–14	M + F	*7.47%*	3.67%	11.52%	*<0.001*
0–14	M + F	*5.87%*	3.36%	8.33%	*<0.001*
0–4	F	−1.92%	−8.33%	5.13%	0.596
5–9	F	*6.93%*	1.41%	12.75%	*0.014*
10–14	F	*5.65%*	0.10%	11.52%	*0.044*
0–14	F	*4.08%*	0.70%	7.57%	*0.018*
0–4	M	6.82%	−0.30%	14.45%	0.061
5–9	M	*6.82%*	0.70%	13.20%	*0.027*
10–14	M	*9.09%*	3.77%	14.68%	*0.001*
0–14	M	*7.68%*	4.08%	11.29%	*<0.001*

Data are presented as lower and upper limits of 95% confidence interval and statistical significance (p). Significant difference is presented in italic values.

19.0/100.000/yr, Montenegro 17.5/100.000/yr, and Poland 16.5/100.000/yr) (20).

The average annual increase in T1DM incidence of 5.87% is considerably lower than 9% estimated previously (16), and is approaching the European average of 3.9% (EURODIAB study, for the period 1989–2003) (17). However, different annual trends in T1DM incidence (0.6–9.3%) have also been reported in European countries, and annual increases similar to one found in Croatian population were also found in Czech Republic (6.7%), Romania (7.8–8.4%), Slovakia (5.1%), Germany (6.5%), Hungary (5.8%), Lithvania (7.2%), and Montenegro (6.5%) (17, 20).

Lower T1DM incidence rates and consequently higher annual increase in incidence in Croatia in the study conducted from 1995 onward could be in a certain extent explained with previously reported changes in socioeconomic status and lifestyle (16, 17). The former study was conducted for the immediate post-war period (Croatian War of Independence 1991–1995), covering transitional years from postwar low-income lifestyle with gradual recovery of living conditions, leading to free inflow of western lifestyle habits. Our study covered the period 20 yr apart from the Croatian Declaration of Independence when lifestyle habits were more stable than in previous transitional period, especially for the younger age groups, and were even more alike to western lifestyle habits. However, one of the reasons may also lay in temporary migration from the war affected regions in the immediate post-war period. It is very likely that

data on newly diagnosed T1DM patients out of their place of residence were lost, resulting in erroneously lower incidence rates, and accordingly higher average annual increase in incidence afterwards.

Parallel with the slowdown in rise of T1DM incidence, we also found flattening of the T1DM incidence trends in the youngest age subgroup (Table 2). As compared to the previous 9-yr period (16), the highest increase in incidence in our study of 7.47% was observed for the 10–14 yr subgroup, followed by the 5–9 yr subgroup with 6.82%. For the youngest age subgroup (0–4 yr), incidence still had an increasing trend of 2.43%, but considerably lower than 14% found previously. For girls in this youngest group the incidence trend was even negative (−1.92%), although not statistically significant (Fig. 1).

Most epidemiological studies conducted in 1980s and 1990s such as EURODIAB (1, 17), Diabetes Mondiale (DIAMOND) Project, and some national studies (21–23), demonstrated an alarming rise in childhood T1DM incidence particularly among the youngest age groups. However, there are several reports with evidence of slowing and leveling of the incidence trends. Finnish national study (14) showed annual increase in incidence of 3.6% until 2005, followed by a plateau until the end of 2011. Similar pattern was observed in Sweden (24) with leveling in incidence during 2005–2007, in particular among 0–4 yr age group. In the Czech Republic (25), a steep average annual incidence rise of 15% during 1996–2001 for the 0–4 yr age subgroup, started to stagnate between 2002 and 2009.

In the recent review of global epidemic of T1DM, Tuomilehto (26) revealed some objections to conclusions of these studies. In Finnish study, the trend data in a post hoc analysis were truncates into three periods and did not provide the full trend analysis over the study period (1980–2011) that would confirm the previously observed 2.5–3.0%/yr increase. Swedish study conducted over 3 yr was considered too short for an adequate trend analysis and the studied population in Czech study was considered too small to exclude random variation in incidence trends.

In any case, it is yet to be determined which factors (most likely exogenous) play crucial role in an increase in T1DM incidence rates. Among several possible causes of this phenomenon, vitamin D deficiency and obesity are one of the most frequently proposed explanations (14, 24, 26). Croatian geographical position in the Mediterranean region provides sufficient sunshine exposure for adequate vitamin D synthesis, for most parts of Croatia, and vitamin D prophylaxis through infancy has been implemented as obligatory supplementation through National prevention program in a dose of 400 U/d during the first year of life and in winter period during the second and third year of life (27). The data on compliance with vitamin D prophylaxis National prevention program for each year are collected by Croatian National Institute of Public Health and are published in Croatian Health Service Yearbook. Thus, in our opinion, vitamin D deficiency could not be endorsed to the increase in T1DM incidence in our population. However, the increasing prevalence of obesity in Croatia (28) might contribute to the increasing incidence of T1DM. According to Croatian Health Service Yearbook, from 2005 to 2010 the number of school-aged children (7–14 yr) with body mass index (BMI) above 90th percentile has increased (from 11.7 to 14% in boys and from 11.0 to 12.3% in girls, respectively) (28). Similar results were obtained from the study analyzing secular changes in body weight, height, and BMI for 1.394 children at the age of 7 in the Splitsko-dalmatinska County, Croatia, from 1991 to 2008, before enrolment at school. They found statistically significant rise in average body weight and BMI and frequency of obesity rose by 1.4 times in boys and 1.7 times in girls from 1991 to 2008 (29). Unfortunately, no data are available on prevalence of obesity in children younger than 7 yr and consequently it is difficult to explain the observed results on increased T1DM incidence in the youngest age group.

Further monitoring is required in order to provide better understanding of the considerable changes in childhood T1DM incidence and trends. Pooling of the data on incidence rates from different populations would provide better understanding of the possible causes of T1DM, and would eventually lead to development of preventive measures for this complex disease.

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