Incidence of childhood-onset Type I diabetes in Slovenia and the Tuzla region (Bosnia and Herzegovina) in the period 1990–1998

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Abstract

Aims/hypothesis. The incidence rate of childhood-onset Type I (insulin-dependent) diabetes mellitus in Slovenian children during the period 1990–1998 was studied and compared to that of children from the Tuzla region (Bosnia and Herzegovina). The secular trend for a 25-year period in Slovenia was also investigated.

Methods. The incidence data were obtained from the national Slovenian Type I diabetes register and from the local Type I diabetes register held in Tuzla. The ascertainment was based on the capture – recapture method and was estimated to be 100 %.

Results. The age-standardized incidence of Type I diabetes mellitus for the age group 0–14 years for Slovenia was 8.54 per 100 000 (95 %-C.I. 7.5–9.5) person-years for both sexes. The incidence for boys was 8.03 per 100 000 (95 %-C.I. 6.7–9.4) and 9.12 per 100 000 (95 %-C.I. 7.6–10.6) for girls. The age-standardized in-

cidence in the Tuzla region was much lower: 3.03 per 100 000 (95 %-C.I. 2.0–4.1) for the whole group, 3.44 per 100 000 (95 %-C.I. 1.8–5.0) for boys and 3.21 per 100 000 (95 %-C.I. 1.6–4.7) for girls. A very low incidence of 0.8 per 100 000 in the youngest age group (0–4 years) was observed in the Tuzla region.

The linear trend of the Type I diabetes incidence rate in Slovenia has been steadily increasing by 3.6 % per year for the last 25 years. The incidence rate in the period 1974–1985 was significantly lower than that in the period 1986–1998 ($p < 0.00026$).

Conclusions/interpretation. Although the incidence rate in Slovenia slightly increased during the period 1990–1998, the incidence rate in the Tuzla region remained at the pre-war level. [Diabetologia (2001) 44 [Suppl 3]: B27–B31]

Keywords Insulin-dependent diabetes mellitus, incidence, secular trends, Slovenia, Tuzla region (Bosnia and Herzegovina).

Childhood-onset Type I (insulin-dependent) diabetes mellitus shows a wide geographic variation [1, 2]. This has been interpreted as evidence of environmental and genetic causal factors. The role of environmental factors is not yet fully understood [3]. Epidemiological studies provide information on the pattern of the incidence of Type I diabetes in different countries and allow a comparison of the incidence in different parts of the world. Thus they offer the possibility of tracing the potential environmental factors that cause Type I diabetes.

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Since 1989, Slovenia has participated in the epidemiological research project for diabetes known as the EURODIAB ACE study [4]. Since 1990, it has also been involved in the WHO DIAMOND project on childhood diabetes [5].

The aim of our study was to determine the incidence of Type I children among Slovenian children and children from the Tuzla region (Bosnia and Herzegovina) in the age group 0 to 14 years during the period 1990–1998 and to compare the data. Special attention was paid to the influence of the war on the primary care of diabetic children and possible changes in the incidence rate in the Tuzla region during this period.

Fig. 1. Geographical location of Slovenia and the Tuzla region (Bosnia and Herzegovina)

Subjects and methods

Geographical and population data. Slovenia is a central European country located between Austria, Italy, Hungary and Croatia (Fig. 1). It has an area of 20 256 km² and a population of 1 978 334 (31st December 1998). The gross domestic product per inhabitant was 8900 EUR in 1998. In 1998 the infant mortality rate was 5.21 per 1000 live births [6].

In 1991 Slovenia proclaimed its independence from Yugoslavia. A brief war with the Yugoslav Army, started on 27th June and ended with the signing of the Brioni Declaration on 7th July 1991. There were 50 Slovene victims during that war.

Bosnia and Herzegovina is a southern European state located between Croatia and Yugoslavia (Montenegro and Serbia) (Fig. 1) with an area of 51 129 km² and a population of 3 459 000 (1991) and 2 898 000 in 1995, after the war. The Tuzla region is situated in the northern part of the Federation of Bosnia and Herzegovina and has an area of 2 909,5 km². Until 1992, the Tuzla region had 973 443 inhabitants (including 277,583 children in the age group 0–14 years). After the war the population decreased: 533 557 inhabitants in 1998 (106 523 children in the age group 0–14 or 39% of the population in 1992). The population in different age groups was estimated based on statistical data for the years 1992 and 1998.

In 1998 the infant mortality rate was 11.7 per 1000 live births. The gross domestic product per inhabitant was 1031 EUR (1998).

In March 1992, Bosnia's Moslems and Croats voted for independence and in April 1992 a war erupted between the Bosnian government and the Yugoslav Army. The war lasted until the Dayton agreement was signed on 21st November 1995. An estimated 329 000 people were killed or disappeared during those 3 years, including 16 853 children. During the war more than a million people escaped to different European countries [7].

Case ascertainment. Type I diabetes subjects were identified after a physician's diagnosis of Type I diabetes as in most diabetes registries [8]. Other inclusion criteria were: the date of the first insulin injection (1st January 1990–31st December 1998) and the age at the first insulin injection (0 and 14 years).

Slovenia. In Slovenia, all children with newly diagnosed Type I diabetes, or suspected diabetes, were referred to the University Children's Hospital in Ljubljana. All patients were residents of Slovenia at the time of the first insulin injection. All data on children with Type I diabetes was registered in the Slovene childhood-onset Type I diabetes register, which is held at the University Children's Hospital in Ljubljana. Currently 860 subjects diagnosed as children with onset of childhood-onset Type I diabetes after 1956 are included in the register. Primary identification was made by the data from this register. A secondary independent sources was data on insulin prescriptions from the Slovene National Institute of Health.

Additionally, patients in the same age group, diagnosed from 1974 to 1989, were identified to calculate the secular trend.

The completeness of ascertainment of registered new cases, based on the capture – recapture assessment [9], was estimated to be 95.7% in the period 1974–1985 and 100% in the period 1986–1998.

Tuzla region (Bosnia and Herzegovina). All children with newly diagnosed Type I diabetes were referred to the University Children's Hospital in Tuzla. All patients were residents of the Tuzla region in Bosnia and Herzegovina at the time of the first insulin injection. The local Type I diabetes register is held at the University Children's Hospital in Tuzla.

Primary case identification was based on the data from this register. Secondary independent sources were data from 14 public health centres in the Tuzla region. The estimated completeness of ascertainment based on the capture-recapture method [9] was 100%.

Statistical analysis. The average incidence rates were calculated as the number of newly diagnosed Type I diabetes patients per 100 000 person-years for the age groups 0 to 4, 5 to 9, and 10 to 14 years. The mid-year populations were used as the denominator (aged 14 years and under). The incidence rate for the whole group (0–14 years) and for the subgroups of boys and girls were also calculated. The 95% -CI were calculated using the Gaussian approximation to the Poisson log-likelihood [1, 10].

Seasonal variability was investigated assuming a sinusoidal pattern over the year. Variations were tested with the chi-square (χ^2) test [11].

Male and female age-specific standardized incidence rates, using a reference population comprising equal numbers in each age-specific and sex-specific group, were calculated [12].

The change in the incidence of Type I diabetes from 1974 to 1998 in Slovenia was estimated by fitting the linear regression with the annual incidence data. The secular trend in Type I diabetes incidence (relative change) was calculated from logarithms of incidence. Linear regression was used, with the regression coefficient being the change per year as a percentage unit [13]. The differences in incidence between the two periods (1974 to 1985 and 1986 to 1998) were tested with the double-tailed *t* test. The male – female differences were tested with the chi-square test (with Yates factor of correction).

Results

Between 1990 and 1998, 299 new cases of Type I diabetes were registered in Slovenia in the age group 0–14 years, and 43 in the Tuzla region. Of these, there

Table 1. Childhood-onset Type I diabetes – age and sex specific crude incidence rates (per 100 000 population), and incidence rates standardized to the world population in children in the age group 0–14 years in Slovenia and the Tuzla region, 1990–1998

Slovenia												
Age group (years)	Boys				Girls				Total			
	Type I patients cases (<i>n</i>)	Population/year (mean)	Incidence rate	95 %-CI	Type I patients cases (<i>n</i>)	Population/year (mean)	Incidence rate	95 %-CI	Type I patients cases (<i>n</i>)	Population/year (mean)	Incidence rate	95 %-CI
0–4	32	54511	6.52	4.2–8.7	27	51669	5.80	3.6–7.9	59	106181	6.17	4.6–7.7
5–9	46	63597	8.03	5.7–10.3	57	60751	10.41	7.7–13.1	103	124349	9.20	7.4–10.9
10–14	64	72315	9.83	5.6–10.7	73	68699	11.80	9.1–14.5	137	141014	10.79	9.0–12.6
0–14	142	190423	8.28	6.9–9.6	157	181119	9.63	8.1–11.1	299	371544	8.94	7.9–9.9
Stand. incidence			8.03	6.7–9.4			9.12	7.6–10.6			8.54	7.5–9.5

Tuzla region (Bosnia and Herzegovina)												
Age group (years)	Boys				Girls				Total			
	Type I patients cases (<i>n</i>)	Population/year (mean)	Incidence rate	95 %-CI	Type I patients cases (<i>n</i>)	Population/year (mean)	Incidence rate	95 %-CI	Type I patients cases (<i>n</i>)	Population/year (mean)	Incidence rate	95 %-CI
0–4	2	21225	1.04	0–2.5	1	20393	0.13	0–1.2	3	41618	0.80	0–1.7
5–9	9	21804	4.59	1.6–7.6	9	20949	4.78	3.7–7.9	18	42753	4.68	2.5–6.8
10–14	11	21724	5.07	1.7–8.4	11	20872	5.26	2.6–7.9	22	42596	5.16	2.8–7.5
0–14	22	64753	3.39	1.8–4.9	21	62214	3.37	1.7–5.0	43	126967	3.38	2.3–4.5
Stand. incidence			3.44	1.8–5			3.21	1.6–4.7			3.03	2.0–4.1

Fig. 2. Incidence of childhood-onset Type I diabetes in Slovenia and the Tuzla region (Bosnia and Herzegovina), 1990–1998

were 156 girls and 173 boys in Slovenia, and 21 girls and 22 boys in the Tuzla region.

Table 1 shows the incidence for boys, girls and the total population in the 3 age ranges (0–4, 5–9, and 10–14 years).

The incidence in Slovenia, directly standardized to the world population, was 8.54 per 100 000 for the whole population (9.12 per 100 000 for girls and 8.03 per 100 000 for boys), and in the Tuzla region 3.03 per 100 000 for the whole group (3.44 per 100 000 for boys and 3.21 per 100 000 for girls).

The male-to-female ratios in Slovenia were 1.18 in the age group 0–4 years, 0.81 in the age group 5–9 years and 0.88 in the age group 10–14 years. In the Tuzla region, the male-to-female ratios were 2.0 in the age group 0–4 years (there were only 2 boys and 1 girl in this group), and 1.0 in both the age groups 5–9 years and 10–14 years. The sex differences were not statistically significant.

In Slovenia the fitted sinusoidal pattern showed a peak of new cases in the late autumn (October–November) and a nadir in late spring (March). However, the observed seasonal variation did not reach statistical significance ($\chi^2 = 3.15$; $df = 2$; $p = 0.06$). In the Tuzla region no sinusoidal pattern or significant seasonal variation was observed.

The crude annual incidence in Slovenia slightly increased during 1990–1998, whereas in the Tuzla region it fluctuated during the war period and returned to the pre-war value in 1998 (Fig. 2).

Moreover, in Slovenia the crude incidence rate in the period 1974 to 1998 constantly increased by 3.6 % per year, based on the linear regression model (Fig. 3). The incidence rates from 1974–1985 were significantly lower than those in the period 1986–1998 ($p < 0.00026$).

Fig. 3. Incidence rate trend in Slovenia for childhood-onset Type I diabetes in the years 1974–1998. Incidence = $0.2442 \times \text{year} + 3.7702$

Discussion

In this study the incidence rates for childhood-onset Type I diabetes in Slovenia and the Tuzla region were compared for the period in which both areas were part of the same country, for the period after proclamation of independence and for the period of war, very short in Slovenia and very long and cruel in Bosnia and Herzegovina. We aimed to compare the trend in the incidence rate in both regions and investigate the influence of the war on the primary care of diabetic children in all age groups.

Data from our study show that the age-standardized incidence rate of Type I diabetes in Slovenia of 8.54 per 100 000 is similar to incidence rates in other Central European countries, for example Hungary 8.8 per 100 000, Austria 9.1 per 100 000, Italy (Lazio region) 8.1 per 100 000, Croatia (Zagreb) 6.8 per 100 000, [2]. The directly standardized incidence rate in the Tuzla region of Bosnia and Herzegovina was lower and was assumed to be 3.03 per 100 000. Demographic data for the period 1990–1998 was difficult to obtain because of the 3-year war. From the present history of Bosnia it is known that during the war a small number of refugees came to the Tuzla region which was closed militarily. Immediately after the war, many people immigrated from the Tuzla region, but many other Bosnians (Moslems and Croats) moved to this region, which clearly influenced the number of new cases in the next few years. In 1998 of newly reported cases of Type I diabetes returned to the pre-war numbers. Although the ascertainment of childhood-onset Type I diabetes in Tuzla region was estimated to be 100% be-

cause insulin was available only at the Central University Hospital, the relatively low incidence, especially in the age group 0–4 years (only two boys and one girl), might be due to unrecognized cases, hidden in the overall number of children who died during the war. Otherwise, the incidence rate in the Tuzla region (Bosnia and Herzegovina) can be compared with the reported incidence in Macedonia 3.1 per 100 000 [2].

In both Tuzla and Slovenia the peak number of new cases occurred in the autumn and winter months. This seems to be similar for the entire Northern Hemisphere [14].

The crude incidence in Slovenia in the period 1986 to 1998 was statistically significantly higher than that from 1974 to 1985. The slight increases in incidence rate observed in the years 1990–1998 have been present throughout the 25-year period of 1974–1998. This has been reported in previous studies in Slovenia: 4.1 per 100 000 in the period 1973–1978, 6.8 per 100 000 between 1983–1988, and 7.59 per 100 000 in the period 1988–1995 [15]. Similar trends have been observed in other European countries [16] but the reasons for this have yet to be explained. In Slovenia the system for the detection and follow-up of newly diagnosed Type I patients has not changed for the last 30 years. The ascertainment also did not change significantly during this period. Thus, the reasons for the increasing incidence of Type I diabetes in Slovenia are not known and can only be speculated upon. It could be possible that a pool of a genetically susceptible subgroup has increased the incidence in the past 25 years more rapidly than in some other surrounding countries, in which such a trend has not been observed. Background HLA and some Type I diabetes HLA susceptible regions (DRB, DRQ) of the Slovenian population could be different to that of the surrounding countries, including those of the people from the Tuzla region [17]. Moreover, the steadily increasing incidence in Slovenia could possi-

bly be ascribed to the gradual transition of Slovenia to the West European lifestyle [2].

In conclusion, the incidence in Slovenia has slightly increased during the observed period of time, while the incidence in the Tuzla region remained at the pre-war level. The fluctuation in the incidence during the 3-year war period was due to the stressful situation, frequent migration, casualties and other related factors.

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