Paediatric and Juvenile Type 1 Diabetes in the Province of Trento. Twenty Years of Observations, from 1998 to 2017

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Abstract

Objectives: The study describes the temporal trend of type 1 diabetes (IDDM) in the 0-29 year's age range in the province of Trento between 1.1.1998 and 31.12.2017, as well as the seasonal and geographical distribution.

Study Design: The source of the cases is represented by the provincial registry of IDDM which is part of the national RIDI (Italian register of insulin-dependent diabetes) network. We retrospectively calculated the distribution of total cases by sex, age class and by year. The trend of the annual incidence rate by age group was represented by a three-year moving average of the rate, to contain the annual fluctuations, considering the relative consistency of the cases. The values of the rates are provided with the relative 95% confidence intervals. The seasonal case trend and geographical distribution are also provided, considering, in particular, the incidence for the urban and the rural area and the altitude levels. The significance of the time trend was analysed using the Cochrane-Armitage criterion and the significance of the differences in proportions was analysed using the chi-squared test. Any seasonal differences were analysed using West & Harrison's dynamic linear model.

Results: Between 1998 and 2017, 421 cases of IDDM have been recorded amongst residents aged 0-29 years (21 cases per year). Males were 53% and the prevalent age range is 0-14 years, which constitutes 67.4% of cases. Rates fluctuate in the first 15 years; they appear stable over the last five years. The average annual incidence rate is higher in the 0-14 age group. Its mean value, considering males and females together, is 18/100,000/year (95% CI: 16.0-20.3) and it increase from 13.0 in 1998 to 17.8/100,000 in 2017. In paediatric age groups, the mean annual incidence rate is higher in 10-14 years. Its value is 20.8/100,000/year (95% CI: 17.2-25.10) and goes from 18.1 in 1998 to 14.6/100,000 in 2017. The number of new cases is higher in the months

November-January but does not appear to be statistically significant. The mean annual incidence rate for the entire 0-29 years age range is slightly higher in rural than in urban areas (16.20 vs 14.0/100,000/year). Excess in rural areas is more evident for the 0-14 age group. The average annual incidence rate is higher among individuals residing in mountainous areas, both overall and for individual age groups. The increase in the incidence rate with the increase in altitude is at the limits of statistical significance.

Conclusion: The incidence of IDDM in the age of 0-29 years seems to have stabilized over the last 5 years. The rate remains always higher in the age of 0-14 y, but decreases over time in the age of 0-4y. The growth of cases in foreign residents may have importance on the trend of the incidence. Excesses emerge in the winter months, in residents in rural and mountain areas. These excesses are not statistically significant.

Introduction

Diabetes is one of the most common chronic diseases of childhood and adolescence and has considerable impacts not only on patients, but also on their families and on medical and healthcare facilities. The most common form amongst children and young adults is type 1 diabetes-IDDM (93%), followed by genetic diabetes (6%) and, in less than 1% of cases, type 2 diabetes [1]. Systematic registration of new cases of the disease is important for being able to describe its distribution and trends, investigate the risk factors and study the healthcare response and the corresponding costs, as indicated by the Italian National Diabetic Disease Plan [2]. The RIDI (Italian Insulin-dependent Diabetes Registry) was established in 1997 to acquire epidemiological data on the new cases of IDDM in the 0-29 years age range, primarily to: coordinate the existing registers and promote new ones, standardise the acquisition and entry of data regarding the incidence of IDDM in the various geographical areas of Italy, create a national database, analyse the time trends for the incidence of IDDM and make available national epidemiological data on the disease. Unfortunately, this initiative, which was innovative for the time, has not been implemented in all areas of Italy [3]. However, the studies produced over time by the RIDI group have made it possible to observe a considerable difference in the incidence of the disease between the various areas involved [3,4], with values 3-4 times higher in Sardinia than in mainland Italy [4]. It was also possible to observe an increase in the disease's incidence over time [5]. This finding is consistent with that of registers conducted in other European countries and in the United States [6-8]. The Trento Provincial Health Authority (APSS) joined the RIDI network in 1997 and in 1998; it initiated data acquisition through the Clinical and Evaluational Epidemiology Service and thanks to the committed cooperation of paediatric and adult diabetes specialists. The study describes the temporal and seasonal trend of IDDM in the 0-29 years age range recorded in the province of Trento between 1.1.1998 and 31.12.2017, as well as the geographical distribution.

Materials and methods

Incident case data was recorded for both the resident and non-resident population of the province of Trento (540,000 inhabitants at 31.12.2017). The latter constitute a very small percentage of total cases, equal to approximately 3% and consequently only the former will be considered. The date of incidence is defined by the date of the first insulin administration. The variables to be acquired for each incident case by the paediatric and adult diabetes specialists were those defined on the standard RIDI sheet, which constitutes the primary information source. Until 2013, the standard sheet was filled out and sent to the Epidemiology service as a paper form; after this date, annual data have been submitted electronically. The completeness of the primary information source was verified using two secondary information flows, namely data regarding co-payment exemption for Diabetes (Code 013) and hospital discharge records, for subjects aged between 0 and 29 years. For those cases identified solely by means of these latter two flows, the diabetes specialists subsequently had to fill out and submit the RIDI sheet. Epidemiology Service retrieved the missing data in order to guarantee the highest possible levels of completeness for the greatest possible number of variables by consulting the Hospital Information System (HIS), a repository which stores all the relevant clinical data for users who came into contact with the Provincial Health Authority's healthcare service. The resident case trend is provided according to gender and age range and class and the age-specific rates are also reported, with 95% CI. The latter are provided as exact annual figures and three-year moving averages, in order to minimise annual variability, considering the relative consistency of the population. The seasonal case trend and geographical distribution are also provided, considering, in particular, the incidence for the urban area (municipality of Trento) and the rural area (the remaining municipalities in the province of Trento) and the altitude levels broken down in accordance with Italian Institute of Statistics (ISTAT) criteria [9] into low-lying areas (up to 300 m above sea level), hilly areas (301-600 m above sea level) and mountainous areas (more than 600 m above sea level). The significance of the time trend was analysed using the Cochrane-Armitage criterion and the significance of the differences in proportions was analysed using the chi-squared test. Any seasonal differences were analysed using West & Harrison's dynamic linear model [10] in order to identify time series of monthly estimates. These analyses were performed using Stata® 16.0 software.

Results

A total of 430 cases of IDDM were recorded, of which 421 in residents. Males prevailed over females (53% vs. 47%) overall and especially in the older age classes. The prevalent age range was 0-14 years, which represented 67.4% of the cases observed over the study period (Table 1). 84% of cases were born in Trento province, 11.7% in other Italian regions and 4.3% were born abroad. In 19.0% of cases at least one parent was born abroad and one in three foreign parents born abroad comes from a country with high migratory pressure. According to the nationality-attribution criteria used in Italy, 52 cases (12.4%) are to be considered foreign nationals and 369 (87.6%) Italian nationals. The average annual number of cases registered over the study period was 21. The trend oscillated greatly until 2011, the year in which the lowest number (14 cases) was recorded; from 2012 onwards, there was an increase in the figure, followed by an apparent stabilisation in the number of new cases recorded each year (Figure 1). The 10-14 years age range is prevalent for each calendar year, whereas the weight of the single age classes varied from year to year without showing any particular time patterns (Figure 2). Across the entire 0-29 years age range, the mean annual incidence rate, considering males and females together, is 13.3/100,000/year (95% CI: 12.0-14.6). The rate increased from 10.8/100,000 in 1998 to 14.1/100,000 in 2017. It is slightly higher in males than in females (13.7 vs. 12.8). For

the 0-14 years age range, the mean annual incidence rate, considering males and females together, is 18/100,000/year (95% CI: 16.0-20.3). The rate increased from 13.0/100,000 in 1998 to 17.8/100,000 in 2017. It is slightly higher in females than in males (18.6 vs. 17.5). For the 15-29 years age range, the mean annual incidence rate, considering males and females together, is 8.5/100,000/year (95% CI: 7.2-10.0). The rate increased from 9.1/100,000 in 1998 to 10.6/100,000 in 2017. It is higher in males than in females (9.9 vs. 7.1). Considering the specific paediatric age classes, in the 0-4 years age range, the mean annual incidence rate, considering males and females together, is 15.2/100,000/year (95% CI: 12.1-18.8) and increases from 8.4/100,000 in 1998 to 16.5/100,000 in 2017; it is higher in females than in males: 16.2 vs.14.3. In the 5-9 years age range, the mean annual incidence rate is 18.2/100,000/year (95% CI: 14.8-22.1) and increased from 13.1/100,000 in 1998 to 22.2/100,000 in 2017; it was higher in females than in males: 22.7 vs.13.9. In the 10-14 years age range, the mean annual incidence rate is 20.8/100,000/year (95% CI: 17.2-25.10) and decreased from 18.1/100,000 in 1998 to 14.6/100,000 in 2017. It is higher in males than in females: 24.7 vs 16.8. The rate's moving average trend per age range shows a higher value throughout the entire study period for the 0-14 years age range (Figure 3); as regards the paediatric age classes, there is a higher overall value for the 10-14 years age class, a decreasing trend for the 0-4 years age class and an increasing trend, from 2007, for the 5-9 years age class (Figure 4). The average age of incident cases across the entire 0-29 years caseload is 11.9 years (st. dev. 7.6); considering the ISPAD age classes (0-18 years) alone, the average age across the entire period is 8.6 years (st. dev. 4.8); the average age for the paediatric age classes (0-14 years) is 7.4 (st. dev. 4.0). By calendar year, the average age drops slightly over time, for all age ranges considered; this reduction does not appear to be statistically significant, even when considering the three-year moving averages.

The proportion of cases of foreign nationality per calendar year increased from 5.9% to 34.9%, with a statistically significant trend (p<0.01) (Figure 5). Overall, these cases are characterised by a lower average age than amongst Italian nationals (10.2 vs 12.1 years). As regards the calendar month of onset, across the entire caseload, the number of cases is higher in the months November-January and this situation is more or less constant for the entire study period. At individual month level, the increase regards the month of January alone. When the data is stratified by age class, this excess regards cases amongst Italian nationals and the 0-4 year's age range in particular, but does not appear to be statistically significant using West & Harrison's dynamic linear models. 22% of resident cases lives in an urban area, namely the municipality of Trento and the remaining 78% in the other municipalities of the province. The mean annual incidence rate for the entire 0-29 years age range is slightly higher in rural areas than in urban areas (16.20 vs 14.0/100,000/year). The age-stratified analysis shows a higher incidence in rural areas that borders on statistical significance, in the 0-14 years age range (23.3/100,000/year). Approximately half (48%) of the caseload lives in low-lying areas, without any significant differences in relation to age class. The average annual incidence rate is high amongst subjects living in mountainous areas, both overall and for the individual age ranges (Figure 6). The increase in the incidence rate observed with the increase in the altitude level is at the limits of statistical significance.
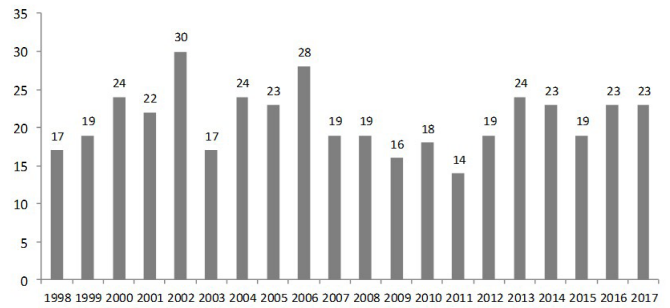

Figure 1: Province of Trento. Cases of paediatric/juvenile diabetes mellitus recorded amongst the resident population aged 0-29 years. Males and Females. Per single year. Period: 1998-2017.
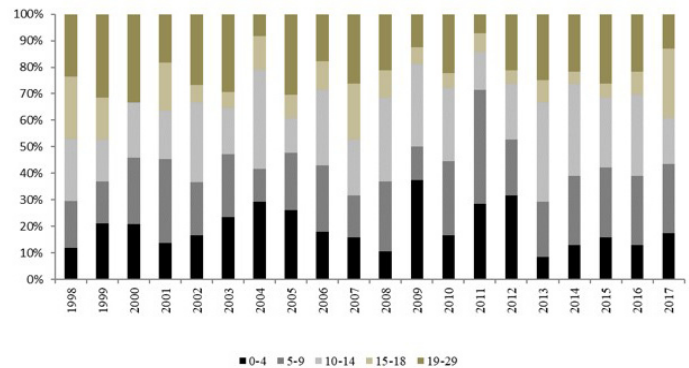

Figure 2: Province of Trento. Cases of IDDM recorded. Proportion by age class and individual year. Males and females. Period 1998-2017.
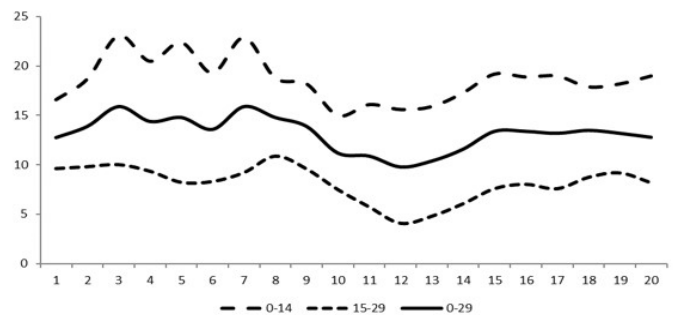

Figure 3: Province of Trento. IDDM incidence rate/100,000. Three-Year Moving Average. Males and Females. By age range. Period 1998-2017.
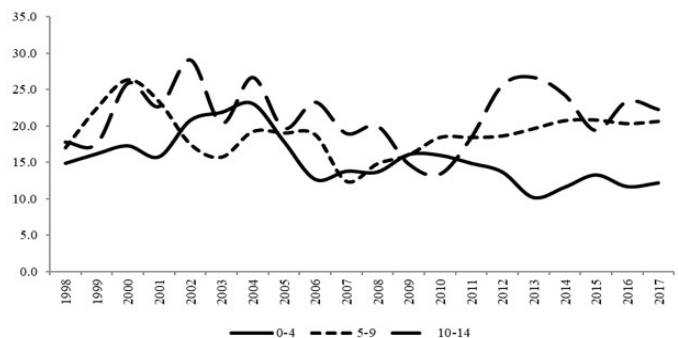

Figure 4: Province of Trento. IDDM Incidence rate/100,000. Three-Year Moving Average. Males and Females. By age class. Paediatric age group. Period 1998-2017.
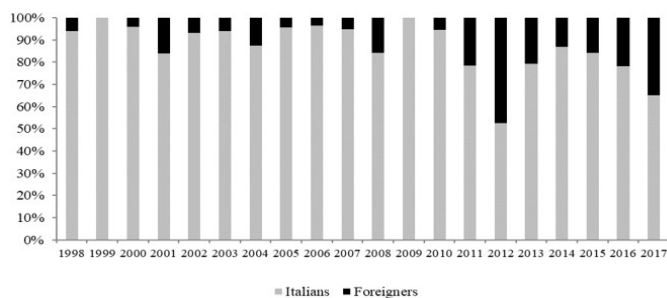
Figure 5: Province of Trento. Proportion of subjects of foreign nationality out of total cases of IDDM recorded in the resident population. Per single year. Period 1998-2017.
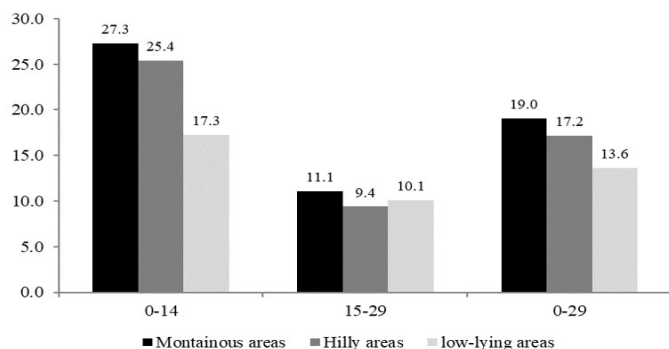

Figure 6: Province of Trento. Average annual incidence rate of IDDM by level of altitude and age class. Period 1998-2017.

Table 1: Province of Trento. Distribution by gender and age class of IDDM cases in the resident population aged 0-29. Period: 1998-2017.

Age class	Males	Females	Total	%	M:F ratio
0-4	39	41	80	19.0	0.95
5-9	38	59	97	23.0	0.64
10-14	65	42	107	25.4	1.55
15-18	23	21	44	10.5	1.10
19-29	58	35	93	22.1	1.66
Total	223	198	421	100.0	1.13

Conclusion

The establishment of the RIDI register made it possible, at local level, by interfacing epidemiological and clinical skill sets, to monitor the IDDM trend over time in the 0-29 year's age range in various areas of Italy, including the province of Trento. At the same time, it was possible to forge alliances with the national RIDI network, with important implications for the training and continuing professional development of individuals involved in local activities [3]. It would be beneficial to strengthen these alliances, at least as regards routine national reporting and in-depth collaboration studies. This would also give greater value to the local data in view also of the current need for health-care facilities to evaluate the quality of care and the diagnostic and treatment pathways for chronic diseases [11]. In order to guarantee complete monitoring, all clinical forms of diabetes should be recorded and not just the type 1 form, in line with the National Italian Diabetic Disease Plan [2]. The cases record-

ed in the province of Trento, matured in over twenty years of data acquisition, allow us to express some considerations on the main trends observed, despite its limited consistency. In absolute terms, the annual number of cases registered has increased over time, reaching two incidence peaks, in 2002 and 2006, followed by apparent stabilisation over the past 5 years. This data does not appear to be influenced by any information bias, considering the integration of multiple information sources throughout the study period. Overall, males prevail over females, especially in the older age classes and approximately 70% of the cases is in the 0-14 year's age range. The average annual incidence rate, especially for the 0-14 year's age range, makes the province of Trento one of the highest incidence areas in Italy, with the exception of Sardinia [4,5]. The incidence rate in the 0-14 years age range remains higher over time than the incidence rate in the other age ranges and, within this age range, incidence increases with the age class, as reported by most studies [6,7,12-17]. Considering the two extremes of the study period, there is an increase in the incidence rates, especially for the 5-9 years age range (+9.1%, equal to +0.45% per year) and for the 0-4 years age range (+8.1%, equal to 0.40% per year). The increase in incidence over time in the province of Trento would appear to be lower than reported in other studies [6-8,16,18-24,29]. The three-year moving average rate suggests that the number of cases has stabilised in recent years, as reported by other studies [12-15,25]. The average age of cases has decreased in almost all age ranges, as reported in other studies [18,20,26,27]. The decrease in age of onset may be due to the increase over time in the number of cases involving foreign subjects, amongst whom the age of onset appears to be lower than amongst Italian nationals [28]. This reduction in age requires close monitoring as a more severe clinical onset is more common amongst younger cases [1,28]. The distribution of cases, especially in the 0-4 years age range, has a certain seasonal pattern, as reported in other studies [18,19,25-29], but does not appear to be statistically significant in our study, most likely due to the limited size of the caseload. Certain variations can be observed between geographical areas, as reported previously [18,19,21,30,31]. In our study, incidence appears to be higher in rural areas, especially in the 0-14 year's age range. There is also a decrease in incidence rate, for all age ranges, from mountainous areas to low-lying areas. On-going monitoring of the disease will make it possible to confirm or disprove the time and territorial trends and will provide the basis of any in-depth studies conducted in the future.

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