



Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes in Subjects Aged 0-29 Years. Twenty Years of Observation in Province of Trento

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Abstract

Objectives: This study describes the time course of ketoacidosis (DKA) at the clinical onset of IDDM in childhood and early adulthood in the resident population of the province of Trento, between 1998 and 2017.

Study design: The source of the cases is represented by the provincial registry of IDDM which is part of the national RIDI (Italian registry of insulin-dependent diabetes) network. The registry includes individual's aged 0-29 years resident in the province of Trento. The criteria used to define DKA are those proposed by the SIEDP (Italian Paediatric Endocrinology and Diabetology Society), namely: DKA is present when pH < 7.30 and/or Bicarbonate < 15 mEq/L. The Hospital Information System (HIS) was used as additional information source in the event that the data on DKA was not present in the case report form. The temporal trend of cases with DKA at clinical onset of IDDM was analyzed, considering sex, age group and citizenship. The factors associated with the presence of DKA at onset and with the severity of DKA were studied using a multiple logistic regression analysis.

Results: Between 1998 and 2017, the Province of Trento RIDI Registry recorded 421 cases of type 1 diabetes amongst residents aged 0-29 years. Males were 53% and the prevalent age range is 0-14 years, which constitutes 67.4% of cases. DKA was present at clinical onset in 39.2% of cases. The proportion of females affected is slightly higher than for males (41.4% vs 37.2%). The DKA temporal trend appears to decrease over time, with a prevalence of 47% in 1998 and of 34.7% in 2017. The decrease appears more evident in Italians than in foreigners. The proportion of cases of DKA is higher in ages 0-4 and in adolescents. The multiple logistic regression analysis indicates that being a foreign national and not having first-degree relatives with IDDM are two independent risk factors for occurrence of DKA at onset of IDDM. The multiple logistic regression analysis shows that pertaining to the lower age classes and being underweight are independent risk factors for the severity of DKA.

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Keywords: Type 1 Diabetes; Ketoacidosis; Risk factors; Ketoacidosis severity; Citizenship.

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Conclusions: The study indicates a decrease in the prevalence of DKA over time; It is statistically significant amongst Italian nationals. Being a foreigner is associated with a greater risk of presenting DKA at the onset of the IDDM, as well as having no relatives with IDDM. The condition of being a foreigner does not weigh on the severity of DKA, unlike younger ages and the condition of underweight.

Introduction

Diabetic ketoacidosis (DKA) is a severe acute complication of diabetes, in particular type 1 diabetes (IDDM) and may present at onset, in subjects (often children and adolescents) who have not yet been diagnosed with the disease, or in individuals who have already been diagnosed with IDDM [1]. DKA at onset, especially in young children, can be the result of either a particular clinical impact of the diabetic disease or of inappropriate or delayed identification or treatment. When it presents during the course of the diabetic disease, it may be the consequence of concomitant or stressor factors, such as, for example, infections, injuries, comorbidities or surgical procedures, or even lacking or incorrect insulin administration [2]. DKA is always a medical emergency, and unless it is promptly diagnosed and adequately treated it can result in high morbidity, mortality and medical costs [1,2]. Children who present with DKA at onset are also more prone throughout their lifetime to difficulties achieving metabolic control and they also have a higher risk of chronic complications than those who do not have DKA at onset of diabetes [3]. The prevalence of DKA at clinical onset of IDDM during childhood and early adulthood varies greatly from country to country [4-6]. In Italy, it has been reported that DKA is present at onset in approximately 40% of new diagnoses in the paediatric population, one of the highest rates worldwide [7]. DKA could however be prevented, or its prevention could be facilitated, by acting on a series of known risk factors [8-10]. This study describes the time trend for the occurrence of DKA at new diagnoses of IDDM in childhood and early adulthood in the resident population of the province of Trento, between 1998 and 2017. It also evaluates the level of association between ketoacidosis at onset with a series of case-related factors, and the factors associated with the severity of DKA.

Materials and methods

The RIDI Registry of the province of Trento (North-Eastern Italy, 540,000 inhabitants at 31.12.2017) is part of the national RIDI network and it is based on a primary information flow, namely the standard RIDI sheet that, until 2013, was submitted by the Diabetes Centres to the Provincial Health Authority's Epidemiology Service as a paper form. Since 2014, annual data are collected in electronic format. The completeness of the primary information source is 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 information flows, the competent Diabetes Centre subsequently has to fill out the RIDI sheet. The Epidemiology Service retrieves any missing data for the specified variables, such as the biochemical status at onset - information that is sometimes not reported in the primary data source - by accessing the Hospital Information System (HIS). This is a repository containing all the relevant clinical data for users who come into contact with the provincial healthcare services. The date of incidence is defined, for each case, by the date of the

first insulin administration. The criteria used to define DKA are those proposed by the SIEDP (Italian Paediatric Endocrinology and Diabetology Society), namely DKA is present when $\text{pH} < 7.30$ and/or Bicarbonate $< 15 \text{ mEq/L}$. DKA is defined as being mild when pH is between 7.2-7.29, moderate when pH is between 7.1-7.19 and severe when $\text{pH} < 7.1$ [10]. As the clinical implications for mild and moderate DKA are similar, these two forms are considered jointly in the in-depth analyses. Temporal trend significance was analysed using the Cochran-Armitage criterion and the significance of the differences between the proportions were analysed using the chi squared test or Fisher's exact test. The factors associated with the presence of DKA at onset and with the severity of DKA were studied by two multiple logistic regression analysis, in which the explanatory variables considered were gender, age class, nationality, country of birth, weight status (normal weight, underweight, overweight/obese), presence of a 1st-degree relative with IDDM, the territorial area of residence (rural vs urban) and altitude of residence (low-lying/hilly/mountainous area). The territorial area and level of altitude were used to estimate the accessibility of diabetes services, based on the assumption that access is more difficult for those living in rural or mountainous areas. The urban area is considered as the municipality of Trento alone and the rural area refers to the rest of the province of Trento; the altitude levels are defined according to Italian Institute of Statistics criteria [11]. The statistical analyses were performed using the Epi-Info package.

Results

Between 1998 and 2017, the Province of Trento RIDI Registry recorded 421 of IDDM cases amongst residents aged 0 - 29 years. Males prevail over females (53% vs 47%) and the prevalent age range is 0-14 years, which constitutes 67.4% of cases (Table 1). The average annual number of cases registered over the study period is 21. The trend oscillates considerably until 2011, the year in which the lowest number (14 cases) is recorded; from 2012 onwards, there is an increase in the figure, followed by an apparent stabilisation in the number of new cases recorded each year (Figure 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 comes from a country with high migratory pressure. There were 52 foreign nationals (12.4%) and of these some 41 (79%) were born in Italy. The proportion of foreign cases recorded increased over time from 5.9% in 1998 to 34.8% in 2017 (chi squared test for trend, $p < 0.0001$). DKA is present at clinical onset in 39.2% of cases (165 subjects). The proportion of females affected is slightly higher than for males (41.4% vs 37.2%); however, this difference is not statistically significant. DKA trend appears to decrease over time, with a prevalence of 47% in 1998 and of 34.7% in 2017. This decrease does not appear to be statistically significant for the caseload considered as a whole (p value for trend = 0.76), but it is significant ($p < 0.05$) when Italian nationals are considered alone (21.4% in 2017 vs 50.0% in 1998). 62% of cases of DKA at onset is concentrated in the 0-14 years age range, with a higher prevalence in the 0-4 year age range, followed by the 15-18 years age range (Table 2), without any differences between males and females. A peak can be observed in the first two years of life, and then gradually decreases with age, followed by a second upturn during adolescence (Figure 3). Multiple logistic regression analysis shows that being a foreign national and having no first degree relatives with IDDM are two independent risk factors for the onset of DKA at diagnosis of IDDM. There is also an excess of risk associ-

ated with adolescence and underweight but the differences are not statistically significant (Table 3). The severity of DKA at onset was calculated on the specific dataset (165 cases). Severe cases represent 17.5% of the case load, without relevant differences from one year to the next and with a slight, non-statistically-significant excess in females (18.3%). Clinical severity is closely age-related, considering that 93% of severe cases occur in the 0-14 year's age range (Table 4). The decrease in the prevalence of DKA with an increase in age is statistically significant (p for trend = 0.0006). The multiple logistic regression analysis shows that pertaining to the lower age classes and being underweight are independent risk factors for the severity of DKA. There is a trend towards greater severity of the DKA in case of residence in rural areas or in mountain areas. However, the differences are not statistically significant (Table 5).

Table 1: Province of Trento. IDDM cases in the resident population. Distribution by gender and age class. 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

Table 2: Province of Trento. Prevalence of DKA at IDDM onset by age class. Males + Females. Period 1998-2017.

Age class	% DKA
0-4	43.7
5-9	36.0
10-14	30.8
15-19	54.5
20-29	40.8

Table 3: Adjusted ODDS RATIO with corresponding 95% CI for the association of a series of specified variables with the risk of DKA at onset of IDDM. Period 1998-2017.

Parameter	Odds Ratio (95% CI)			p value
Females vs males	1.09	0.72	1.67	0.66
5-9 years vs. 0-4 years	0.70	0.37	1.31	0.26
10-14 years vs. 0-4 years	0.60	0.32	1.11	0.10
15-18 years vs. 0-4 years	1.71	0.79	3.68	0.16
19-29 years vs. 0-4 years	0.94	0.50	1.77	0.86
Foreign nationals vs Italians	2.16	1.17	3.98	0.01
No relatives with IDDM vs relatives with IDDM	2.72	1.14	6.49	0.02
Underweight vs normal weight	1.73	0.96	3.10	0.06
Overweight/obese vs normal weight	0.79	0.44	1.41	0.42
Residence in rural area vs urban area	1.18	0.69	2.01	0.53
Residence in low-lying vs hilly/mountainous area	1.00	0.73	1.38	0.97

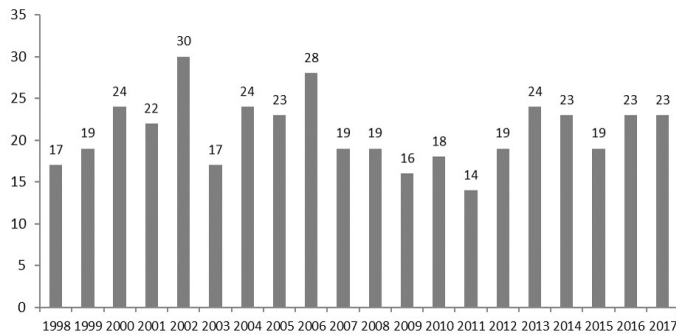


Figure 1: Province of Trento. IDDM cases recorded amongst the resident population aged 0-29 years. Males and Females. By single calendar year. Period 1998-2017.

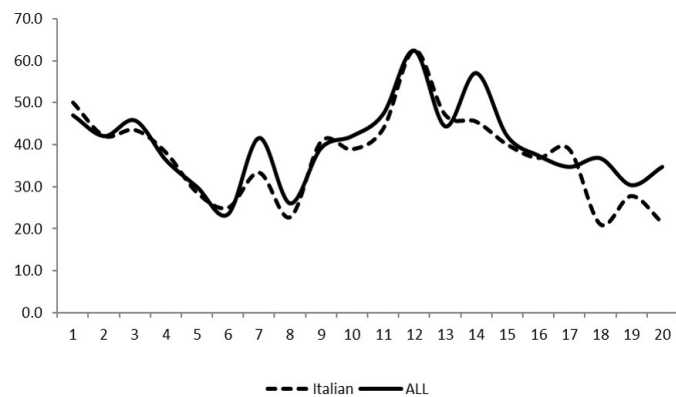


Figure 2: Province of Trento. Proportion of cases with DKA at onset of IDDM in subjects aged 0-29 years. Males and Females. Total and amongst Italian nationals. By single calendar year. Period 1998-2017.

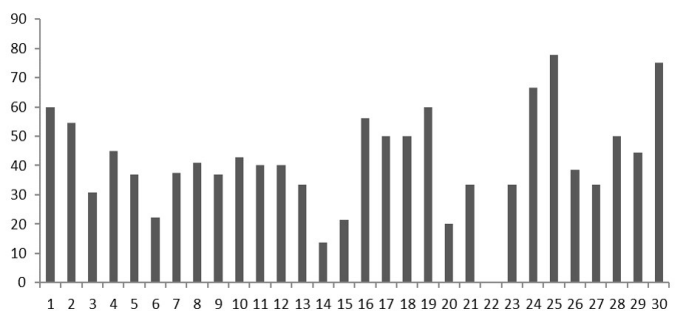


Figure 3: Province of Trento. DKA prevalence at onset of IDDM. Males and females. By single year of age. Period 1998-2017.

Table 4: Province of Trento. Severity of DKA at onset of IDDM by age class. Period 1998-2017.

Level of ketoacidosis	Age class					Total
	0-4	5-9	10-14	15-19	20-29	
Mild/moderate	68.6	71.4	81.8	95.8	97.4	82.5
Severe	31.4	28.6	18.2	4.2	2.6	17.5

Table 5: Adjusted ODDS RATIO with corresponding 95% CI for the association of a series of specified variables with the risk of severe DKA at onset of IDDM. Period 1998-2017.

Parameter	Odds ratio	95% CI		p value
Females vs males	0.53	0.19	1.50	0.234
10-14 years vs 15-29 years age classes	4.38	0.77	24.94	0-095
5-9 years vs 15-29 years age classes	12.07	2.24	64.98	0.003
0-4 years vs 15-29 years age classes	13.55	2.60	70.54	0.002
Foreign nationals vs Italians	0.51	0.14	1.81	0.299
Relatives with IDDM vs NO relatives with IDDM	0.65	0.05	7.79	0.738
Underweight vs normal weight	3.93	1.29	11.93	0.015
Overweight/obese vs normal weight	0.61	0.11	3.19	0.561
Residence in rural area vs urban area	0.77	0.18	3.12	0.715
Residence in hilly/mountainous vs low-lying area	2.28	0.74	6.98	0.146

Discussion

The prevalence of DKA at clinical onset of IDDM in children and young adults varies from 13 to 80% in the various countries for which reliable data regarding the incidence of diabetes are available [4-6]. This variability may be associated with the overall quality of the medical management of IDDM, but is also influenced by the degree of awareness and knowledge of the characteristics of the disease, especially amongst parents and general practitioners [2,10]. Correct and timely recognition of the symptoms presenting at onset of the disease may allow effective patient management before DKA develops, thus leading to a reduction in its frequency. This could be facilitated by the presence of nationwide networks that share the criteria and procedures for the management of children and young adults with IDDM [12,13]. The province of Trento has a higher incidence of IDDM in subjects aged 0-29 years than the average value for mainland Italy [14] and presents, according to the findings of this study, prevalence values for DKA at clinical onset that are in line with those reported by previous Italian and European studies [7,15-19]. The study indicates a decrease in the prevalence of DKA over time that reaches a trough in 2015 (15%), before increasing to 34.7% in 2017. The decrease over time is only statistically significant amongst Italian nationals. The new increase in the prevalence of DKA in recent years could be attributed, at least in part, to the increase, amongst the cases included in the registry, of foreign nationals, who reached a higher proportion (34.8%) precisely in 2017, the year in which the greatest difference was observed in the prevalence of DKA at onset between foreign and Italian nationals (50.0% vs 21.4% in Italian nationals). Foreign subjects are in any case at higher risk of DKA at onset, a fact that could be associated with a different clinical impact of the disease according to ethnic origin [10,15,16,20-23]. It must also be taken into consideration that social and cultural barriers may affect the knowledge and awareness of the disease and access to healthcare services, considering also the lower prevalence of IDDM in their or their parents' countries of birth [2,4,6,10]. As regards distribution by age, there is an early DKA peak in the first two years of life, in line with the findings of previous studies [2,4,5,8-10], followed by peaks between 16 and 19 and 24 and 29 years of age. The peaks amongst younger children may be associated with the biological characteristics of the IDDM and the potential difficulties in obtaining effective differential diagnosis with other more common acute illnesses

of early childhood [10,20]. In adolescents and young adults, a higher frequency of DKA may be associated with poorer knowledge or awareness of diabetes in this age group, which may result in delayed diagnosis [20,21]. In addition, in this study, the later peaks may have been emphasised by the limited number of cases in our registry amongst these age classes. The occurrence of DKA does not show any significant differences regarding the residence of subjects defined according to the type of area and the level of altitude, which suggests a homogeneous distribution of healthcare and IDDM management criteria throughout the province. This study confirmed an excess amongst underweight subjects and that a protective role is played by the presence of a first-degree relative with IDDM [10,20,21,24]. While confirming the protective role of the presence of first-degree relatives with IDDM, the multiple analysis reiterates that DKA at onset correlates closely with being a foreign national. Being a foreign citizen does not seem to have an impact on the severity of the DKA. The multiple analysis indicates that the independent risk factors on the severity are lower age and being underweight. DKA can be averted when the disease is diagnosed and treatment is initiated at an early stage. Unfortunately, it is not possible to establish with certainty the average time that elapses between the onset of the first symptoms due to hyperglycaemia alone and DKA. In some cases, this period is very short, especially in very young children. Initial management of diabetic patients by facilities with specialised and skilled staff can reduce delays in diagnosis and result in the initiation of more appropriate treatment [3,12,13]. The adoption of existing guidelines and their correct application in clinical practice remain the fundamental premises for the prevention and control of this phenomenon at population level [4,5,10,25].

Conclusion

In conclusion, a diabetes case registry represents a fundamental tool for monitoring the distribution of the disease over time and space but it can also provide important insights into the clinical features of the disease at onset and on the quality of management at the population level.

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