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Research paper

Epidemiology of Type 1 diabetes mellitus in Cyprus: rising incidence at the dawn of the 21st century

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ABSTRACT

OBJECTIVE: The incidence of Type 1 diabetes mellitus (T1DM) in Greek-Cypriot children aged less than 15 years between 1990 and 2009 was examined along with gender differences concerning the age of onset and the seasonal variation at manifestation of the disease. DESIGN: All newly diagnosed cases of T1DM in children less than 15 years old were registered with the capture-recapture method from 1990 until 2009. RESULTS: The overall mean annual incidence during these 20 years is 12.46 per 100,000. A comparison of the incidence between the two decades (1990-1999 *vs* 2000-2009) indicated a rising trend, from 10.80 per 100,000 person-years during the first decade to 14.44 per 100,000 person-years during the second decade. There was an overall male predominance (M/F: 1.05), which is in agreement with the male predominance in the population less than 15 years of age, except for the group who manifested T1DM at ages 10-15 years where females prevail. The percentage of children who developed T1DM at ages 0-5 years in the total T1DM population increased in the second decade (26.4% *vs* 19.0%), and significantly more children were diagnosed during the cold months as opposed to the warm months ($p<0.001$). CONCLUSION: The incidence of T1DM in Cyprus is rising. The identification of causative environmental factors will theoretically explain this phenomenon and new preventive strategies can therefore potentially be developed.

Key words: Epidemiology, Incidence, Type 1 Diabetes Mellitus

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is one of the most common endocrine metabolic disorders in children and adolescents worldwide. T1DM incidence varies greatly between different countries, within countries, and between different ethnic populations.[1] The highest incidence is observed in Scandinavian countries, among which Finland has the highest reported prevalence, while a gradual decrease is noted in countries located closer to the equator.[2-4]

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This north-south gradient is interrupted by some Mediterranean regions, such as Sardinia which has an unexplained high incidence.[5] The lowest incidence in the world is observed in China although there exist large geographic variations of populations at risk.[6]

Today, the incidence of T1DM is plainly on the increase throughout the world and it is estimated that it may reach the status of a pandemic by the mid-21st century.[7] A large number of studies have been published clearly confirming the rising incidence of T1DM, especially in the younger age groups,[8-14] and this is of the greatest concern. This trend is intimately associated with an increasing influence of environmental trigger factors operating against a background of genetic susceptibility. If these trends continue, the number of new cases of Type 1 diabetes mellitus in children younger than five years of age may double in some regions between 2005 and 2020, with cases in children under 15 years rising by 70%[15] among the total of T1DM population. The underlying mechanisms responsible for the rise of T1DM, especially in the younger age groups, remain unclear, while in the meantime the autoimmune nature of T1DM continues to be under investigation.[16,17]

The main purpose of the present study was to illustrate the temporal trend of the incidence rate of T1DM during the 20-year period 1990–2009 among Cypriot children less than 15 years of age. We also report gender and age distribution of incidence and seasonal variation during the study period, which may help in the identification of contributing factors of the disease.

MATERIALS AND METHODS

Subjects and research design

The study was carried out in a group of 374 children and adolescents aged 0-15 years diagnosed in accordance with the criteria of the American Diabetes Association (http://www.ispad.org/NewsFiles/IDF- ISPAD_Diabetes_in_Childhood_and%20 Adolescence_Guidelines_2011.pdf) during the period 1990-2009. Informed consent was obtained from both of the parents or guardians of all children and adolescents participating in the study. The completeness of ascertainment was calculated according to the capture-recapture method.[18] Patient records from (a) paediatric departments of all state hospitals of the island and (b) private sector physicians and diabetologists were the first source of ascertainment. The second independent source was the Cyprus Diabetes Association (CDA), as all T1DM children on the island are required to register with the CDA in order to obtain medication and devices free of charge. Therefore, we hypothesize that we have identified the majority of paediatric patients with new-onset T1DM.

The data characterizing the Cypriot population were quoted in the Demographic Annual reports by the Department of Statistics and Research of the Ministry of Finance (http://www.mof.gov.cy/mof/cystat/statistics.nsf/index_en/index_en). An annual estimation of the population under the age of 15 years was made, taking into account births, deaths and net migration.

The inclusion criteria for the current study were the following. (i) The patient had to be of Greek-Cypriot origin. Turkish-Cypriots were not included in the study due to the current political situation. Other immigrant minorities were excluded because of the differences in their genetic and environmental status. (ii) Diagnosis of T1DM was based on clinical (polyuria, polydipsia, weight loss) and laboratory findings (fasting blood sugar level >125 mg/dl, glycosuria, ketonuria, frequent metabolic acidosis, absent C-peptide, elevated Hb A1c and in almost all cases positive GAD antibodies). (iii) Insulin treatment at onset and thereafter. (iv) Aged 0-15 yr at the time of diagnosis. (v) Exclusion of monogenic diabetes based on family history. The information collected included: (i) name, (ii) gender, (iii) date of birth, (iv) date of diagnosis and (v) family history of T1DM.

Statistical analysis

Annual cases of T1DM are reported along with the annualized incidence of new cases per 100,000 population under 15 years old, assuming a Poisson distribution with 95% confidence intervals (CI). The graphical representation of the annualized incidence was smoothed with a 3-year simple moving average in order to enable detection of time trend of the incidence of T1DM.

The age at diagnosis of new T1DM cases was grouped into the three standard age groups of 0 to 4

yrs, 5 to 9 yrs and 10 to 14 yrs. New cases (with 95% CI) are presented in relation to these age groups separately for the two decades of the study, and the three groups in each decade were compared assuming a binomial distribution. Male to female (M/F) ratio was calculated overall and within age groups and compared to the M/F ratio of the population less than 15 years of age.

Grouping of cases according to the month and season of diagnosis did not reveal any consistent pattern of periodicity. Therefore, another grouping of cases was selected in order to reflect local climatic differences throughout the year based on the average temperature record on the island as follows: November, December, January and February were defined as cold months (average temperature 14.2 ^{0}C), October, March, April and May as neutral months (average temperature 22.5 ^{0}C) and June, July, August and September as warm months (average temperature 31 ^{0}C) [*http://www.cyprus-weather.com/article_cyprus-average-temperatures-c*]. Differences in the newly diagnosed T1DM between age groups and season groups were compared assuming a binomial distribution.

Age at diagnosis across age groups and decade of diagnosis was computed. Because the distribution of age across groups did not show equal variances, the non-parametric Mann Whitney U test was used for these comparisons.

In all tests p values <0.05 were considered as statistically significant. All analyses were performed using R statistical software, version 2.13.0.

RESULTS

Incidence

The incidence of T1DM during 1990-1999 reported previously was 10.80/100,000.[19] During the 20-year period (1990-2009), a total of 374 children with new onset T1DM meeting the inclusion criteria were identified resulting in an overall incidence of 12.46/100,000 of our population. Twenty-seven subjects out of 374 (7.2%) reported a first-degree relative with T1DM. New cases of T1DM and overall annualized incidence per 100,000 person-years with 95% confidence intervals for the population below the age of 15 yr are presented in Table 1. The annual incidence is presented in Figure 1, where data were smoothed using a simple moving average of three years in order to determine time trend. As is shown, a relatively constant incidence occurred from 1990 to 1999, after which there is an increasing trend up to 2005, followed by a similar trend thereafter.

In order to document the increasing trend we compared the incidence between the two decades (1990-1999 *vs* 2000-2009) of the study period. The incidence increased from 10.80/100,000 (95% CI 9.21, 12.58) during the first decade (1990-1999) of the study up to 14.44/100,000 (95% CI 12.53, 16.55) during the second decade (2000-2009, $p<0.001$). The annual frequency of newly diagnosed cases of T1DM and corresponding incidences per 100,000 person-years and 95% confidence intervals (95% CIs), overall and stratified by decade, were estimated, assuming Poisson distribution. In both decades and overall, the incidence of T1DM per 100,000 person-years was lower in the younger age group (0 to 4 years of age) compared to the older age group (10-14 years of age), as shown in Table 2. Overall it was lower compared to the 5-9 years age group in the second decade. The incidence of T1DM per 100,000 person-years was higher in the second decade compared to the incidence in the first decade in all three age groups but this difference proved statistically significant only for the 0-4 and 5-9 year-olds.

Age of Onset and Gender Differences

There is a non-significant prevalence in the total number of males to that of females resulting in a male to female ratio of 1.05, which is in agreement with the gender ratio M/F = 1.06 in the general population under the age of 15 years *(http://www.mof.gov.cy/mof/cystat/statistics.nsf/index_en/index_en)*. The median age of onset for females was higher than that of males (9.25 *vs* 7.68 yr; $p=0.034$). The median age at T1DM onset does not differ by gender for children aged 0-4 years old (p-value$=0.450$) or for children aged 10-14 years old (p-value$=0.691$), although the mean age at DM onset differs by gender (higher for females) for children aged 5-9 years old (p-value$=0.010$). Similarly, the median of age at diagnosis did not differ between the two decades: 9.25 years (1990-99) vs. 8.25 years (2000-09, $p=0.186$).

Table 1. Newly diagnosed cases of type 1 diabetes mellitus and annual incidence per 100 000 population with 95% confidence interval (CI)

Year	Population age<15 years	Cases			Overall annual incidence per 100,000 person years	95% CI
		Overall	Males	Females		
1990	151,600	15	6	9	9.89	5.53, 16.33
1991	154,300	16	8	8	10.36	5.92, 16.84
1992	157,200	16	8	8	10.19	5.81, 16.53
1993	159,600	14	6	8	8.77	4.79, 14.72
1994	161,600	21	9	12	13.00	8.04, 19.87
1995	161,400	18	10	8	11.15	6.60, 17.63
1996	161,700	16	7	9	9.89	5.65, 16.07
1997	161,100	20	13	7	12.41	7.57, 19.18
1998	159,400	15	10	5	9.41	5.26, 15.53
1999	154,697	15	6	9	9.53	5.41, 15.60
2000	157,300	26	13	13	16.72*	10.79, 24.23
2001	151,700	21	9	12	13.84	8.57, 21.17
2002	149,200	13	4	9	8.71	4.64, 14.91
2003	146,200	32	15	17	21.89***	14.95, 30.91
2004	146,000	19	10	9	13.01	7.83, 20.33
2005	141,200	17	11	6	12.04	7.01, 19.29
2006	139,800	24	16	8	17.17**	10.99, 25.55
2007	137,900	15	11	4	10.88	6.08, 17.95
2008	136,400	20	6	14	14.66	8.94, 22.65
2009	135,000	21	14	7	15.55	9.63, 23.78
overall		374	192	182	12.46	

*,**,*** Comparison with year 1990 annual incidence assuming Poisson distribution, *p=0.015, **p=0.010, ***p<0.001.

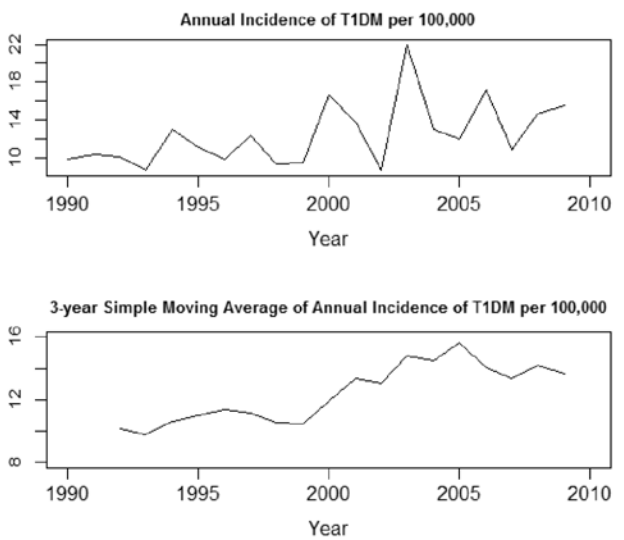

Figure 1. Three year simple moving average of annual incidence of T1DM per 100,000.

Figure 2 presents the ratio of males and females with DM1 diagnosed in the time period 1990-2009 in relation to the age of onset, expressed as age group in accordance with the international standards. Although the overall M/F ratio is comparable with that of the general population, it is clear that males predominate in the age group 0-4 years and females in the age group 10-15 years.

Seasonal variation

The newly diagnosed cases were classified into three groups based on the average temperature recorded on the island. Overall, more children were diagnosed with T1DM during the cold months (November, December, January, February) compared to the warm months (June, July, August, September) (p=0.004), whereas no difference was observed in the

incidence between neutral (October, March, April, May) and cold months throughout the study period (1990-2009), as depicted in Table 3. This difference between cold and warm months was also statistically significant for the first decade (1990-99, p=0.031), but not for the second decade.

DISCUSSION

Global reports based on large epidemiologic studies demonstrate an increasing incidence of T1DM, by 2% to 5%, and this is especially evident among young children.[15,20-22] Between 1990 and 2000 the incidence rate of T1DM in Cypriot children and adolescents was 10.76/100,000.[19] Interestingly, within the subsequent five-year period, i.e. between 2000-2004, a statistically significant increase was observed in Cypriot children and adolescents with the incidence rising to 14.9/100,000.[23] Our findings during the 20-year period (1990-2009) suggest that the overall prevalence of T1DM is increasing in Cyprus and is currently at 12.46/100,000; the largest increase is seen in children less than five years of age, which is consistent with previously published data.[8,10,11,13,24,25]

Lifestyle changes over time may account for the increasing incidence rates between 1990 and 2009, it being well established that environmental factors have a significant effect on the pathogenesis of T1DM and are highly likely to contribute to the increasing incidence rates in our registry. Specifically, a recent report of 5-year changes in the prevalence of overweight and obesity in 11-year old children in Cyprus documented increasing rates of obesity among school-aged children, especially in girls and children living in rural areas.[19,23,26] In addition, a positive correlation between nitrate levels in water and incidence of T1DM has also been reported.[27-29] However, although various environmental factors have been strongly implicated, genetic factors cannot be excluded. Significantly, it has been proposed that T1DM develops due to intrauterine and postnatal exposure to factors that interfere during the development of autoimmunity.[30] Nevertheless, since the precise pathomechanistic viral cytotoxic pathway inducing destruction of pancreatic β-cells remains elusive, the search for identification of T1DM etiopathogenesis factors is still the subject of numerous research projects.

Data on the average age of onset of T1DM in females *vs* males revealed no significant differences. We found a non-significant predominance in the total number of males to that of females, which is in agreement with the overall male predominance. Moreover, we found a higher increase of the incidence of T1DM in children under the age of five years, with the highest rate in boys, whereas females predominate during the peripubertal period. We assume that male gender is a risk factor for early manifestation of the disease, whereas pubertal hormones contribute as a stress triggering event taking into account the gender difference in pubertal development. Recent studies noted that this gender disproportion was also observed in other European countries[8,31,32] and North America[33] and that the manifestation of the disease occurs earlier in boys than girls. A male excess is found primarily among Caucasoid populations,[34] while in African populations it is more prevalent in girls.[35]

Patterns in the seasonal variation with regard to the month of diagnosis of T1DM have been reported. A seasonal pattern in the onset of T1DM with increased cases during late autumn, winter and early spring has been repeatedly confirmed in the young.[36] Using data from all the patients in the present study there is an obvious seasonal variation during the 20-year period. There is an uneven distribution of diagnosed T1DM cases throughout the year, with significantly increased onset during the winter months of January (37 cases) and February (52 cases). This supports the hypothesis that during colder months infections may act as precipitating factors in the clinical manifestation of the disease by possibly accelerating autoimmune processes.[37]

In summary, we have shown that the incidence of T1DM in Cyprus is rising. Further research is needed to delineate the pathogenic mechanisms responsible for the observed increase in the incidence of childhood diabetes. Moreover, such research will clarify whether this increase is mainly due to environmental or exclusively to a genetic background, or both. If such factors are ultimately linked with T1DM, they might prove useful in the development of future therapies for the disease or they may lead to additional treatment therapies and thus contribute to the improvement of the patient's quality of life.

Table 2. Incidence of T1DM in relation to age group and decade of diagnosis per 100,000 person years with 95% CI, assuming Poisson distribution

	Age Group (years)					
	0-4		5-9		10-14	
Period at Diagnosis	n	Incidence (95% CI)	n	Incidence (95% CI)	n	Incidence (95% CI)
1990-1999	31	5.95 (4.04, 8.45)	66	12.30 (9.51, 15.66)^{ff}	66	12.50 (9.66, 15.91)^{ff}
2000-2009	55	12.82 (9.66, 16.70)*	77	16.23 (12.81, 20.29)*^{,f}	76	14.23 (11.20, 17.81),
1990-2009	86	9.06 (7.24, 11.19)	143	14.15 (11.91, 16.67)^{f,ff}	142	13.37 (11.26, 15.70)^{ff}

*,** P values for comparing incidences of between the two decades within each age-group *p<0.001 *f*
^{f,ff} P Values for comparison with the 0-4 year age group within each decade and overall, ^{f} p=0.046, ^{ff} p<0.001

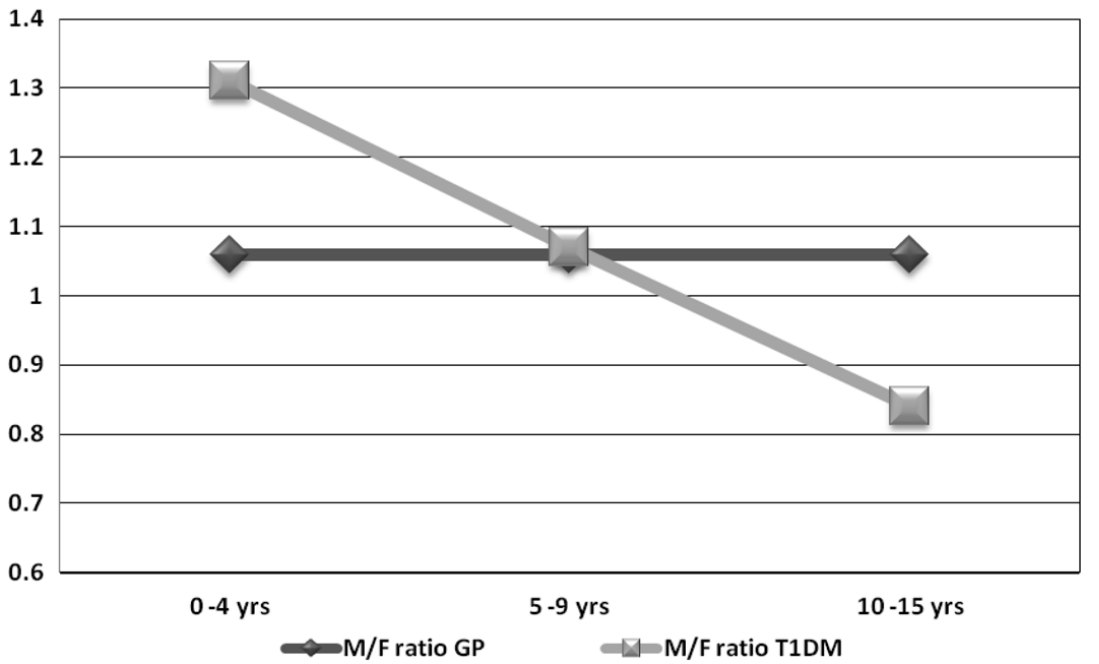

Figure 2. The male to female (M/F) ratio in the three age groups of the general population (GP) under 15 years of age and in T1DM (DM) children at the time of diagnosis.

Table 3. Months *f* specific newly diagnosed cases of T1DM and incidence with 95% CI in the two decades

	Month at Diagnosis					
	Cold Months		Neutral Months		Warm Months	
Period at Diagnosis	n	% (95% CI)	N	% (95% CI)	n	% (95% CI)
1990-1999	64	38.6 (31.1-46.4)	61	36.7 (29.4-44.6)	41	24.7 (18.3-32.0)***
2000-2009	82	39.4 (32.7-46.4)	67	32.2 (25.9-39.0)*	59	28.4 (22.3-35.0)**
1990-2009	146	39.0 (34.1-44.2)	128	34.2 (29.4-39.3)	100	26.7 (22.3-31.5)***

^{f} see methods for definition
*, **, ***, **** Binomial comparisons assuming Binomial distribution against: "Cold Months" group: * p<0.05, ** p<0.01, ***p<0.001

Conflicts of Interest: *The authors declare that they do not have any conflicts of interest and no financial relationships that might have influenced the present work.*

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