Incidence of type 1 diabetes in age groups above 15 years: facts, hypothesis and prospects for future epidemiologic research

Incidence of type 1 diabetes in age groups above 15 years: facts, hypothesis and prospects for future epidemiologic research

Bruno G[1], Gruden G[1], Songini M[2]

[1]Dept. of Medical Sciences, University of Turin, Italy

[2]Diabetes Unit, Cagliari, Italy

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Corresponding author and author to receive reprint request:

prof. Graziella Bruno, University of Turin, Department of Medical Sciences

Corso Dogliotti 14, I-10126 Turin, Italy

Tel: +39 11 633 6709

Fax: +39 11 6634 751

Email: graziella.bruno@unito.it

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Abstract

Although onset of type 1 diabetes can occur in adulthood, epidemiological data are scarce, limiting our potential to identify unknown determinants of the disease. Paucity of registres expanding the recruitment of incident cases up to adulthood, atypical clinical features of type 1 diabetes at onset, misclassification of type 1 as type 2 diabetes, little use of markers of β-cell autoimmunity represent major obstacles in studying the risk of type 1 diabetes in adults.

New strategies in study design, data collection, and analyses may overcome these problems in the future. Population-based surveys and registries including adulthood; use of etiological rather than clinical criteria to define type 1 diabetes; availability of electronic health records as prescription data sources to avoid missing data, and application of proper statistical methods will be instrumental to gain better insight on the epidemiology and natural history of the disease.

Epidemiological and immunological studies have substantially increased our current knowledge on the incidence rate and the natural course of type 1 diabetes (1-5). Most epidemiological studies have been performed in childhood-onset type 1 diabetes; however, sparse incidence data are also available in people of 15 years and over at diabetes onset, showing that the disease occurs at higher rate than it was previously thought. In this commentary, we will summarize available epidemiological data on adult-onset type 1 diabetes, discuss difficulties in collecting accurate incidence data and suggest new directions for future research in this field.

AUTOIMMUNE TYPE 1 DIABETES: ONE OR MANY?

Destruction of pancreatic β-cells leading to insulin deficiency is the hallmark of type 1 diabetes. The most common type 1 diabetes subtype (type 1a) has an autoimmune pathogenesis and both a genetic predisposition and auto-antibodies (ICA, IAA, GAD65, IA-2, ZnT8) are often present (4). Onset of the disease occurs typically in children/adolescents, but the disease can develop at any age (1). Adult-onset type 1 diabetes might be characterized by a longer asymptomatic period before clinical diagnosis, better preservation of residual β-cell function, and lower frequencies of multiple auto-antibodies as compared to type 1 diabetes diagnosed in childhood/adolescence (6-10). Because of the less severe loss of insulin secretion, the disease deviates from the classical phenotype at presentation and can even resembles type 2 diabetes. In adults, the subgroup with an even slower progressive autoimmune diabetes has been defined as latent autoimmune diabetes of adults (LADA) (13-18), and has an impact on the collection of reliable epidemiological data on type 1 diabetes in adults (15-17). Indeed, 5-10% of patients with adult-onset diabetes are non-insulin-requiring at onset and demonstration of diabetes-associated autoantibody is required for differential diagnosis (11-12).

INCIDENCE RATES OF TYPE 1 DIABETES: THE RELEVANCE OF REGISTRIES

Type 1 diabetes incidence varies greatly between different geographical areas and ethnic groups. Large multicentre studies, such as the EURODIAB and the DIAMOND, have clarified the epidemiology of type 1 diabetes over geographical areas and time (19-22). The highest incidence rate is observed in Northern European countries, particularly in Finland, and in the Mediterranean island of Sardinia ("hot spot"), while China has the lowest risk (23). In childhood, there is a fairly equal incidence of type 1 diabetes among men and women, except in Sardinia where the risk appears greater in men (24). Worldwide there is a trend for an increasing incidence of type 1 diabetes. This increase is lower in areas at higher risk of diabetes compared to those at lower risk and a plateau/declining risk has been observed in Finland, Sweden and Norway (26-28). This may be due to annual fluctuations in incidence rate; however, if confirmed over a longer span of time, it might also suggest a depletion of genetically susceptible individuals in the highest risk areas and/or a reduction of environmental determinants. Of interest, the incidence of type 1 diabetes appears to increase most in children at age 0-4 years (4.0% per year) than in children at age 10-14 years (2.1% per year) (21). However, the SEARCH study showed that in the United States incidence increased in in all ages <20 years but not in the youngest age group 0-4 years (29).

A concerted effort to compare epidemiological data from youth- and childhood-onset type 1 diabetes was performed in 1996-1997 by nine EURODIAB centres, representing geographical areas with different risk of type 1 diabetes among children (high risk: Sardinia and Sweden, intermediate risk: England, Antwerp, Belgium and Catalonia, Spain; low risk: Lithuania, Bucharest, Romania and Slovakia) (30). The standardized incidence in the age group 15-29 years varied from 4.8 to 13.4 per 100,000 person-years. The study showed that geographical differences mirrored those of childhood registries, with the highest risk in Finland and Sardinia. However, the number of youth-onset cases in each centre was quite low, ranging from 17 in Belgium to 238 in Sweden, and there was a low completeness of ascertainment compared to that achieved in childhood registries (70 to 90% vs. 93-100%). In the United States the SEARCH study is registering since 2002 the incidence of type 1 diabetes in youth <20 years of age, covering a population at risk of almost 5.5 million

people in six centers (29). Incidence rate in young adults 15-29 years of age was 13.4/100,000 in period 2002-2009, almost two-fold lower than in age 0-14 years.

In Europe, comparison of data among children and adults showed that the risk of type 1 diabetes falls steeply after 15 years of age in the areas with a high incidence in childhood, such as in Finland (31), while it declines more gradually with increasing age in areas with lower risk, such as Lituania (32) and Italy (33). A systematic review has recently summarised the results of surveys and on-going population-based registries that estimated incidence rates of type 1 diabetes in adults (34). Most studies (9, 29-33, 35-46) used two sources of ascertainment and applied the two-sample capture-recapture method to estimate missing cases (47-48) (Table 1); however, the numbers of incident cases, identified by each source and 95% confidence limits surrounding estimates, were seldom reported.

Several studies have shown a male predominance in patients with youth/adult-onset type 1 diabetes at variance with childhood-onset type 1 diabetes (30, 49-50). This is surprising as autoimmune diseases are more likely to affect women. The underlying cause is unknown; however, sex differences in exposure to environment type 1 diabetes triggers and/or in hormonal/genetic susceptibility may represent possible explanations.

Only few studies extended the recruitment of incident cases long enough to allow temporal trend analyses. Studies from Sweden (37-38) and Belgium (43-44) reported a shift towards younger age at onset, providing a possible explanation for the increasing childhood-onset type 1 diabetes incidence observed by most registries worldwide. These data would be consistent with “the spring harvest hypothesis” (51), which basically suggests that the increasing incidence trend, observed in the younger subgroup of the population covered by registries, might have been mirrored by a corresponding reduction in adult incidence with the final result that the lifetime cumulative risk of the disease might have not changed over time. In other words, a more rapid progression of type 1 diabetes in susceptible individuals, rather than a more frequent initiation of the disease, would have been behind the rise of type 1 diabetes in children. However, data from Finland (31), UK (40) and

Italy (33), which expanded collection of incident cases up to adulthood, do not support the hypothesis of a shift towards childhood as the main explanation of the increasing temporal trend of the disease in children. Indeed, in Italy increasing trends were similar in children and adults (3% per year) and incidence rates were stable in the group with 15-29 years of age (period 1991-99) in the UK and in the group with 15-39 years of age (period 1992-96) in Finland. Moreover, previous published studies on the incidence of type 1 diabetes in adults from Sweden had a very low completeness of ascertainment and a recent study has shown that the real incidence in adults up to 34 years of age was two to three times higher than previously reported (39).

Besides difficulties in data collection, epidemiological and definition pitfalls may represent important limitations in the study of adult-onset type 1 diabetes epidemiology and state-of-art epidemiological analyses are recommended to minimise biases and maximise the value of collected information.

EPIDEMIOLOGICAL PITFALLS

Missing cases and Estimated Completeness of Ascertainment

Type 1 diabetes is relatively rare and the incomplete ascertainment of incident cases in the target population can profoundly affect precision of estimated risk. To overcome this problem, the EURODIAB and the DIAMOND studies required participating centres to estimate the number of missing cases and the completeness of ascertainment using the capture-recapture method. This method was originally developed by wildlife and fisheries biologists to estimate the size of animal populations and was then applied by epidemiologists to estimate the occurrence of various diseases or conditions (i.e. illegal drug addicts, people infected with HIV etc.) (47-48). Basically, incomplete lists of affected people, such as hospital records and prescription data sources, are matched and overlapping subjects in the two different sources used to estimate the overall number of cases in the population and thus the number of missing cases (Figure 1). The ratio between the observed and the estimated number of affected people provides the estimated completeness of ascertainment. The

computations are easy to perform and the method has gained great popularity, particularly in the field of diabetes epidemiology (52-53). Recently, three nationwide Swedish registers [the National Diabetes Register (NDR), the Diabetes Incidence Study (DISS), and the Prescribed Drug Register (PDR)] were reassessed separately and collectively by means of a capture-recapture method in order to evaluate the validity of previous reports and to estimate new incidence rates (39). The Authors found that incidence rates were two to three times higher than previously reported. Moreover, ascertainment in the DISS was only ~29% (2007–2009) and thus much too low to ensure reliable epidemiological data.

It is important to underscore that the capture-recapture method is based on assumptions, such as independence of data sources, equal probability of listing in each source, and constant probability of ascertainment over time, that are often violated in human diseases and in diabetes as well (54). Therefore, the estimated completeness of ascertainment may be erroneously high despite an elevated number of missing cases. For instance, in the study mentioned above, the NDR and the DISS were both based upon the active notification of incident cases by nurses and clinicians. This increased the likelihood that incident cases identified by one source were also identified by the other source (positive dependence) and the large number of overlapping cases biased downward estimates of missing cases, incorrectly suggesting high level of accuracy of estimated incidence (Figure 1). On the other hand, completeness of ascertainment may also be underestimated. Applying the capture-recapture method on multiple data sources (NDR, DISS, PDR) to estimate the total number of incident cases, the PDR data source resulted to have allowed the identification of only 70% of estimated numbers of cases. This appears a quite unrealistic estimate as patients cannot receive insulin in Sweden without having been entered in the PDR and hence the PDR registry should identify all individuals with type 1 diabetes. Misclassification (type 2 referred as type 1 diabetes) and heterogeneities of patients in the NDR probably biased upward estimate of missing cases in the PDR registry, leading to an underestimation of ascertainment completeness.

Collapsing dependent sources and log-linear models incorporating first-order and higher-order interaction terms (39, 53) may be applied to model both dependence between sources and heterogeneities of patients among sources, such as age, treatment, severity of the disease, socioeconomic conditions, in order to reduce the bias in the prediction of the number of missing cases, but substantial variations among estimated numbers of cases make sometimes difficult to correctly interpret the results (54).

In the near future, the increasing availability of electronic health records will provide new exiting opportunities for epidemiological research on adult-onset type 1 diabetes incidence, making estimation of completeness of ascertainment obsolete (55-57). Patients over 19 years of age with type 1 diabetes onset may not require hospitalization, depending on local organization of diabetes care, making more difficult their identification through hospital discharges. However, continuous insulin-treatment since the time of diagnosis is a tracer condition for type 1 diabetes; therefore, prescription data source should allow to identify all incident cases occurring in the population. Previous experiences with the prescription data source showed a bimodal pattern of incidence with a first peak close to puberty and a second peak in the fifth decade of life, likely due to misclassification of type 1 with insulin-treated type 2 diabetes (58-59). On the other side, enrichment of the prescription data source with clinical and laboratory datasets may further enhance classification accuracy. Moreover, the prescription data source might be employed to automatically exclude patients with a previous therapy with oral drugs and/or insulin treatment as likely affected by type 2 diabetes.

Anticipation of age at onset over time or cohort effect

Age at onset of multi-factorial diseases such as type 1 diabetes might be an indicator of the strength of genetic susceptibility. In Finland, the cumulative incidence of type 1 diabetes in offspring decreased in parallel with increasing age of diabetes onset among parents (60). In Italy, the effect of having parents of Sardinian heritage on the risk of having type 1 diabetes was higher in children than in adults (61). An heterogeneity by age at onset in socioeconomic indicators has also

been found, which might suggest a different role of environmental determinants in different age groups (62-63). However, the most intriguing data on heterogeneity by age at onset are those on changes in temporal trends of type 1 diabetes incidence among age groups. Most studies assessing incidence temporal trends in children showed a greater increase over time in the youngest age group and this might suggest an increasing effect over time of an environmental determinant, affecting preferentially the 0-4 year age group.

However, temporal trends can be influenced not only by the age of diabetes onset (age effect), but also by the period of onset (period effect) and the date of birth (cohort effect) (64). As these three time scales are interrelated (date of birth plus age at diabetes onset correspond to calendar year of onset), advanced statistical methods, such as age-period-cohort analysis, are required to help discriminate their relative contribution and avoid result misinterpretation. Indeed, a shift towards younger age at onset over time might also result from an increased incidence of type 1 diabetes in cohorts of children, who were born in the same period and had thus been exposed to the same environmental risk factors (cohort effect). Therefore, a cohort effect might be erroneously interpreted as a shift towards younger age at onset if appropriate statistical methods are not used (64). Moreover, distinguishing between “period” (variation over time period or calendar years that affect all age groups simultaneously) and “cohort” effects (changes across age groups in subjects who were born in the same years) may help generate hypothesis on the underlying environmental risk factors involved. A non-linear “period” increase would suggest an abrupt exposure to an environmental determinant, while a non-linear “cohort” increase might be consistent with the effect of epidemic of congenital infections or other environmental factors affecting the perinatal age.

The age-period-cohort analysis uses hierarchically ordered multivariate models that are compared by the likelihood ratio test and allow the evaluation of non-linear components of “period” and “cohort” effects as well as assessment of the drift, which is a linear variation of the incidence in time. Unfortunately, when the incidence increase is linear, it is impossible to distinguish between the effects of period and birth cohort. For instance, an analysis of the Registry of Turin, Italy, in the

period 1984-2003 for the age group 0-29 years found a linear effect only, which could not be ascribed to either the calendar period or the birth cohort effect (33). Similarly, the Danish registry found a continuous steeper increase for birth cohorts after 1985 that showed no sign of levelling off, but this trend could not be separated in an increased risk by birth cohort or period (65).

In the future, incidence registries of type 1 diabetes should be organized in order to allow the assessment of temporal trend in a wider age span. At present, most of studies assessing temporal trend in incidence rates limited the analyses to 0-14 years of age and thus did not allowed to capture the total effect of time variations in the whole population (24, 65-72). However, if periods of registration are quite long and models fitted using continuous variables (64), age-period-cohort analysis may be applied to avoid misinterpreting a cohort effect as an anticipation in age at onset (age effect).

DEFINITION PITFALLS

Misclassification of type 1 as type 2 diabetes is the main problem affecting studies on the epidemiology of type 1 diabetes in adults (16). The concept of heterogeneities of diabetes has increasingly been used when referring to diabetes classification (see recent reviews on this issue 14-15), which may apply not only to adulthood, but also to childhood diabetes. The spectrum of clinical presentation of type 1 diabetes in adults - although based on an autoimmune process - is broad, ranging from acute onset to LADA. As a matter of fact, we cannot exclude the working hypothesis that the risk for type 1 diabetes might be higher in adulthood in those countries where risk is low in childhood and potentially caused by different determinants. Therefore, the critical question is to assess the true impact of type 1 diabetes in adults on the cumulative incidence of the disease. If LADA patients, who have still preserved β-cell function allowing oral anti-diabetic treatment, are considered as affected by type 1 diabetes, it is likely that more adults than children will result to be affected by autoimmune diabetes and this finding might open a new interesting scenario in the study of determinants of the disease. On the other side, if only insulin-treated cases are registered (73) incidence rates might be biased downward with an heterogeneity depending on

bias by indication, that is the variable attitude of diabetologists to prescribe insulin treatment, the so called “clinical inertia”. The group with the highest heterogeneity and risk of misclassification is the 30-40 years age group and future studies should mainly focus on identification and correct classification of incident cases in this age group. It should be noticed that the relative proportions of type 1 versus type 2 diabetes depends also on the characteristics of the underlying population, being quite low in areas where the prevalence of obesity is high, as in the USA, and higher in areas with lower prevalence of overweight, such as in China. In Italy, we previously showed that among normal-weighted subjects aged 30–54 years at the onset of diabetes, as much as 50% had at least one marker of β-cell autoimmunity and could be defined as autoimmune diabetes, though only 52% of them were insulin-treated (74). Studies focusing on young adults arising in the population identified through the prescription data source would allow to capture most incident cases of diabetes. In all of these subjects markers of β-cell autoimmunity should be examined and type 1 diabetes defined independently of the rate of β-cell failure and initial treatment. Two population-based studies conducted in Sweden (75-76) and in Turin, Italy (11), have described the incidence of type 1 diabetes defined according to this approach. In the Turin population (2 million inhabitants, period 1999-2001), autoimmune diabetes was defined as permanent insulin treatment or a fasting C-peptide level ≤0.20 nmol/l or ICA or GAD antibody positivities, and rates were based on 143 incident cases in people aged 30-49 years identified with 95% completeness of ascertainment. Out of them, 13% only were defined as having type 1 diabetes, but this proportion ranged from 30% in those aged 30–34 years to 8% in those aged 45–49 years. Incidence rates/100,000 person-years was 7.3 (95% CI 6.2-8.6) in the age group 30-49 years, slightly lower than classical type 1 diabetes in age 15-29 years (7.1, 95% CI 6.6–7.0). In the Kronoberg population (75-76), Sweden (177,000 inhabitants, period 1998-2001), autoimmune diabetes was defined as fasting C-peptide level ≤0.25 nmol/l or ICA or GAD antibody positivities. Rates were based on 109 incident cases in people aged ≥20 years. Incidence rate was 27.1/100,000 person-years (95% CI 25.6-27.4) in people aged 20 years and more. This two-step approach (identification of all young adults with incidence of

diabetes and screening for markers of β-cell autoimmunity in all cases) should be performed by a central Registry with the collaboration of both diabetologists and general practitioners, depending on local health care organization. Although expensive, this project should be considered a project priority in epidemiologic research of diabetes, and therefore performed at international level with standardized methods.

CONCLUSIONS

Type 1 diabetes is an autoimmune disease, with age-related variability in β-cell failure progressing to insulin-dependence, so that etiological criteria, i.e. based on positivities of markers of β-cell autoimmunity, rather than clinical criteria, i.e. based on clinical presentation at diabetes onset, should be applied in adults to better define the type of diabetes. Surveys and registries extending the registration of incident cases up to young adults, independently of their initial treatment, would have more chance to increase our knowledge on incidence, temporal trend and determinants of the disease than studies limited to childhood diabetes and those relying on prevalent diabetes in adults. Electronic health records, such as prescription data sources are available in many countries, allowing to overcome the problem of missing incident cases. The heterogeneity of the disease in young adults, which makes it difficult to sharply define different clinical entities among patients, should be overcome by the assessment of markers of β-cell autoimmunity in all young adults with incident diabetes, independently of their clinical features at disease onset. Hopefully, in the near future, both researchers and funders companies should attempt to establish population-based registries extending the recruitment of cases up to adulthood, through the definition of standardized methods of data recruitment and analyses, in analogy with the landmark EURODIAB and DIAMOND projects for childhood diabetes. The final aim is to perform comparative analyses among geographic areas and to suggest hypothesis on the unknown determinants of the disease.

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Table 1: Main studies of incidence rates of type 1 diabetes in people aged 15 years and over. Completeness of ascertainment and 95% confidence intervals (CI) of incidence rates as reported by each study

	Age at onset (years)	Period	Incident cases (n)	Rates/100,000 person-years (95% CI)	Estimated completeness of ascertainment	References	Comments
Denmark	30+	1973-77	1240	8.2	99%	58	Retrospective cohort of insulin-treated patients stratified into Type 1 (16.2%), insulin-treated (54.1%) and short-term treated (29.6%) diabetes
Norway	15-29	1978-1992	784	17	90%	36	Two-fold increased risk with respect to previous decades
Sweden	15-34	2007-09	3016	25.2	95%	39	Four data sources were employed, obtaining two-fold higher rates than previously estimated.
Finland	15-39	1992-96	1388	15.9 (15.1-16.8)	88%	31	Four sources of ascertainment, male/female ratio=1.7
UK	15-34	1991-2008	1437	12.1	?	41	Incident cases identified through the General Practice Research Database
Belgium	15-39	1989-03	427	9.0 (8.1-9.9)	92%	44	Anticipation in age at onset in boys but not in girls
Lithuania	15-34	1991-2008	1591	8.3 (7.9-8.7)	87%	32	Risk was relatively stable over 1991-2008 Male/female ratio=1.7
Catalonia, Spain	15-29	1996-97	316	10.9 (9.7-12.3)	90%	30	Survey as part of the EURODIAB Study
Austria	15-29	1994-96	66	7.1 (5.5-9.0)	87%	42	Male/female ratio=1.6
Turin, Italy	15-29	1984-2003	650	7.1 (6.6-7.7)	93%	33	Increasing trend in both children and adults (3% per year)
	30-49	1999-2001	92	4.7 (3.8-5.8)	99%	11	Subgroup of patients with typical type 1 diabetes
Sardinia	15-29	1996-97	104	12.5 (10.3-15.2)	70%	30	Survey as part of the EURODIAB Study
Libia	15-29	1981-90	176	11.9 (10.3-13.8)	95%	45	Two sources of ascertainment
United States	17-35	2002-08	1074	14.10	?	46	The Defence Medical Surveillance System was employed to identify incident cases among active

							components of US Armed Forces
	15-19	2002-09	714	13.4	95.3%	29	Non-Hispanic White. Temporal increase over time
	18-44	1990-2005	2918	17.5		73	Insulin-requiring diabetes Two-fold higher incidence in black

Table 2: Summary points on incidence of type 1 diabetes in adults

What is already known
1. Incidence of type 1 diabetes is higher in children than in adults
2. Sex differences in risk are more evident in adults than in children, with 50-70% higher risk in males than in females
3. The strength of genetic susceptibility is higher in children than in adults
4. Temporal trend is increasing in children, is either stable or increasing in young adults
5. The residual β-cell function is higher in adults than in children
Topics requiring further studies
1. What is the incidence of autoimmune diabetes and LADA in adults ?
2. What is the pattern of risk in the elderly?
3. Is the incidence of autoimmune diabetes higher in adults living in geographical areas with lower risk for childhood type 1 diabetes?
4. Are there similar geographic differences in childhood and adulthood type 1 diabetes?
5. Is the incidence of type 1 diabetes in adults increasing non linearly by birth cohort or period?
6. Are determinants of type 1 diabetes similar among age groups?
Critical points
1. Standardization of criteria to define autoimmune diabetes in adults recruited by population-based registries, independently of clinical features at diabetes onset.
2. Feasibility of population-based registries of autoimmune diabetes in adults in different geographical areas.
3. Feasibility of laboratories routinely assessing markers of β-cell autoimmunity and linked to population-based diabetes registries.