# Epidemiology, Clinical Aspects, and Biology of IDDM Patients Under Age 40 Years

## Comparison of data from Antwerp with complete ascertainment with data from Belgium with 40% ascertainment

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**OBJECTIVE** — To compare the incidence rate of IDDM in the age-groups 0–14 and 15–39 years in Antwerp, Belgium, and to compare demographic, clinical, and biological data from Antwerp IDDM patients with 92% ascertainment with those from a larger Belgian patient group with 40% ascertainment.

**RESEARCH DESIGN AND METHODS** — Incident cases of IDDM were reported by physicians of the Belgian Diabetes Registry and in Antwerp by several other sources. In Antwerp, completeness of ascertainment was calculated by the capture-recapture method. Demographic and clinical data were collected by questionnaire. Blood was sampled for HLA-*DQ* genotyping and, in new-onset patients, for autoantibodies.

**RESULTS** — In Antwerp, the age- and sex-standardized IDDM incidence rates were similar in both age-groups (0–14 years: 11.8/100,000; 15–39 years: 8.9/100,000). The incidence rate decreased in girls above age 15 years (6.9/100,000; $P = 0.003$) but not in boys (11.0/100,000). Both in Antwerp and Belgium, IDDM was diagnosed more frequently in the 15–39 years age-group (60% of all cases) than under age 15 years, with a lower prevalence of acute symptoms, ketonuria, high-risk HLA-*DQ* genotype, and autoantibodies against insulin, islet cells, and IA-2, but with a higher prevalence of GAD65 autoantibodies.

**CONCLUSIONS** — In Antwerp, the incidence rate of IDDM under age 15 years is intermediately high compared with the rates in other European regions. It is similar in the 15–39 years age-group, but with a marked male predominance. Demographic, clinical, and biological data show the same age-dependent heterogeneity as the data collected nationwide, with 40% ascertainment indicating the representativeness of the latter.

Diabetes registries operating according to standardized rules are a useful instrument to study epidemiological aspects of diabetes (1,2). Most studies on IDDM have been performed in the age-group 0–14 years (3–5), since diagnosis of this form of diabetes is more straightforward in that age category. However, it is important to study older age-groups as well, since there are indications that a non-negligible number of cases, if not the majority, arise at adult age (6–10). Some reports have described a second incidence peak in late adulthood arising around 50–60 years (8,11–13), apart from the well-known peak around puberty (4). Several diabetes registries have extended their age range above age 15 years (6,14–23); it thus became more evident that IDDM is a heterogeneous disease in terms of demographic and clinical presentation (6,10,12, 13,17–19,23).

Since 1989, we have collected demographic, clinical, and biological data from newly diagnosed IDDM patients, aged 0–39 years, in the Antwerp district, a geographically well-defined region in the northern part of Belgium that represents ~9% of the Belgian population in that age category. Over the same period, the same parameters were also determined for the same patient category in the Belgian population for which ascertainment was incomplete (estimated at 40 vs. 92% in the Antwerp region). The present study reports the incidence rate of IDDM in the Antwerp region during a 7-year period (1989–1995), comparing the age-groups 0–14 and 15–39 years. In addition, the population-based demographic, clinical, and biological characteristics of the Antwerp IDDM patients are compared with those of the larger group of Belgian IDDM patients to investigate whether the findings with an estimated ascertainment of 40% can be considered as representative for the entire Belgian IDDM population. In both populations, these characteristics were compared between the age-groups 0–14 and 15–39 years.

## RESEARCH DESIGN AND METHODS

### Criteria for entry into the Belgian Diabetes Registry

Prospective entry of newly diagnosed diabetic patients into the Belgian Diabetes Registry (BDR) was based on the nationwide voluntary reporting by pediatricians and endocrinologists participating in the BDR. Individuals were diagnosed as having IDDM

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**Abbreviations:** BDR, Belgian Diabetes Registry; GAD65-Ab, autoantibody against the 65-kDa isoform of GAD; IA-2-Ab, IA-2 autoantibody; IAA, insulin autoantibody; ICA, islet cell autoantibody; JDF, Juvenile Diabetes Foundation.

according to the criteria of the National Diabetes Data Group (24). Patients who met the criteria for diagnosis of IDDM were entered in the present study if *1*) insulin treatment was started at the time of registration before their 40th birthday and between 1 January 1989 and 31 December 1995, and 2) the patient was residing in Belgium for at least 6 months. The date of diagnosis was equated with the date of first insulin injection, according to international recommendations (1). A questionnaire was filled in and blood was sampled for genetic analysis. Samples taken at clinical onset (i.e., before start or within the first 7 days after start of insulin treatment) were also analyzed for autoantibodies. On the occasion of annual follow-up visits, questionnaires were filled in to validate the clinical classification of IDDM at onset. Clinical follow-up data were available for 932 of 1,469 IDDM patients (63%) recruited during the period 1989–1995. Only 3 of these 932 patients (0.3%) became permanently insulin independent during follow-up and were excluded from the study. Because the ascertainment of IDDM patients by the registry is not complete throughout Belgium, incidence rates for the disease were determined in the Antwerp district, a geographically well-defined region in the northern part of Belgium.

### Incidence study in the Antwerp district

The Antwerp district, situated in the northern part of Belgium, comprises 30 urbanized municipalities, covering a total area of 1,000 km$^2$, with an average yearly population density of 927 inhabitants per squared kilometer (25). This region has a sea climate with an average yearly temperature of 4°C in winter and of 18°C in summer (26). The annual rainfall ranged between 636 and 907 mm (26). The yearly average population size, aged 0–39 years, during the period 1989–1995 was around 500,000 and was based on the yearly civil registration numbers (27).

In accordance with EURODIAB ACE (Europe and Diabetes: Aetiology of Childhood Diabetes on an Epidemiological Basis) criteria (4), IDDM patients were included in the incidence study if they fulfilled the criteria outlined for enrollment in the BDR and if they resided in the Antwerp district for at least 6 months. Clinical follow-up data were available for 201 of 342 patients (59%) initially classified as having IDDM during the period 1989–1995. One patient was later reclassified as having NIDDM (1/201 or 0.5%) and was excluded from the study.

About 75% of the new IDDM cases were ascertained prospectively on the basis of voluntary reporting by pediatricians and endocrinologists participating in the BDR. The other 25% were obtained through pediatricians and endocrinologists of the Antwerp district, who did not collaborate directly with the registry. They were contacted yearly by mail and asked to fill in retrospectively an anonymous questionnaire. The physicians who did not respond were contacted by telephone. They were also asked to collect, whenever possible, a blood sample from the reported IDDM patients for HLA-*DQ* genotyping. If sampling occurred before start or within the first 7 days after start of insulin treatment, autoantibodies were also determined.

The completeness of primary ascertainment in the Antwerp district was validated by a combination of three secondary sources: general physicians, diabetes nurses, and the local branch of the Flemish Diabetes Association, a patient association which provides various services (e.g., information, training, summer camps, disposables) to its members. The ascertainment rate amounted overall to 92%, with a 98% rate in the age-group 0–14 years and 85% for ages 15–39 years. The incidence data of the age-group 0–14 years were obtained within the framework of the EURODIAB ACE study (4).

### Biological markers

Insulin autoantibodies (IAAs), autoantibodies against GAD65 (the 65-kDa isoform of GAD) (GAD65-Abs), and antibodies to IA-2 (IA-2-Abs) were determined by liquid phase radiobinding assay (6,28) and islet cell autoantibodies (ICAs) by indirect immunofluorescence using cryosections of human pancreases (6). Receiver operating characteristic analysis (29) was applied to data from 789 healthy control subjects and 693 recent-onset IDDM patients to assess the cutoff value for positivity for IAA (≥0.6% tracer bound), ICA (≥12 Juvenile Diabetes Foundation [JDF] units, corresponding with an endpoint titer of ≥1/20), GAD65-Ab (≥2.6% tracer bound), and IA-2-Ab (≥0.4% tracer bound). All assays performed consistently well during repeated participation in external quality control programs (Immunology of Diabetes Workshops, University of Florida proficiency testing, European Nicotinamide Diabetes Intervention Trial serum exchange).

HLA-*DQA1* and *-DQB1* genotyping was performed by polymerase chain reaction amplification of genomic DNA, followed by dot-blot hybridization with allele specific probes (30). The latest nomenclature of the World Health Organization committee for factors of the HLA system was used (31).

### Statistical analysis

Age- and sex-specific incidence rates were calculated from the number of newly diagnosed IDDM patients per 100,000 inhabitants per year. The denominator of the incidence rate over the 1989–1995 period was the sum of the population sizes for each calendar year (27). To facilitate comparisons with other countries, directly standardized rates (32) were calculated using a standard population comprising equal numbers of cases in each of the age- (5-year intervals) and sex-specific categories. The 95% CIs were computed assuming a Poisson distribution of the observed number of cases (33). Completeness of ascertainment was estimated by the capture-recapture method (34), which assumes ascertainment of the same catchment population by using a combination of multiple secondary sources. By cross-classifying cases according to their presence or absence in the primary and secondary sources, respectively, the degree of completeness can be estimated. Poisson regression models (35) were used to study differences in incidence rates according to age, sex, calendar years, and interactions among these variables. Statistical significances of differences were computed by the $\chi^2$ test for prevalences and by the Mann-Whitney test for median values.

**RESULTS** — During the period 1989–1995, 341 new IDDM patients under age 40 years were diagnosed in the Antwerp district yielding an average annual standardized incidence rate of 10.0/100,000 (95% CI 9.0–11.1). Although the standardized incidence rate of IDDM tended to be higher among the population under age 15 years, <40% of the IDDM patients aged 0–39 years were diagnosed before that age (Table 1). The total incidence rates (0–39 years) did not change between calendar years.

Table 2 shows the annual incidence rates in the Antwerp district by 5-year age-groups and by sex. The total incidence rate varied significantly by age. Under age 15 years, the overall annual standardized incidence rate in girls was similar to that in

**Table 1—*Standardized incidence rates (per 100,000) of IDDM by year and age in the Antwerp district***

| | 0–14 years | | 15–39 years | | 0–39 years | |
|---|---|---|---|---|---|---|
| Year | Cases | Incidence rate (95% CI) | Cases | Incidence rate (95% CI) | Cases | Incidence rate (95% CI) |
| 1989 | 17 | 10.8 (6.3–17.4) | 34 | 10.2 (7.0–14.2) | 51 | 10.4 (7.8–13.7) |
| 1990 | 15 | 9.3 (5.2–15.4) | 34 | 10.0 (6.9–14.0) | 49 | 9.8 (7.2–12.9) |
| 1991 | 15 | 9.5 (5.3–15.6) | 27 | 8.0 (5.3–11.7) | 42 | 8.6 (6.2–11.6) |
| 1992 | 17 | 10.4 (6.1–16.7) | 30 | 9.0 (6.1–12.9) | 47 | 9.5 (7.0–12.7) |
| 1993 | 22 | 13.5 (8.4–20.4) | 35 | 10.6 (7.4–14.8) | 57 | 11.7 (8.8–15.1) |
| 1994 | 26 | 15.8 (10.3–23.1) | 25 | 7.5 (4.8–11.1) | 51 | 10.6 (7.9–13.9) |
| 1995 | 21 | 12.8 (7.9–19.5) | 23 | 7.0 (4.5–10.6) | 44 | 9.2 (6.7–12.3) |
| 1989–1995 | 133 | 11.8 (9.8–13.9) | 208 | 8.9* (7.8–10.2) | 341 | 10.0 (9.0–11.1) |

Poisson regression analysis (35): *$P > 0.05$ vs. 0–14 years age-group. The total incidence rates of IDDM in the 0–39 years age-group did not change from year to year.

boys but, unlike in boys, it decreased significantly thereafter. As a result, the male-to-female ratio was 0.9 (62/71) under age 15 years but rose significantly to 1.7 (131/77) between age 15 and 39 years ($P < 0.005$). In agreement with the data in Antwerp, a similar excess of adult male patients was observed in the total Belgian IDDM population (0–14 years: male-to-female ratio, 290/291 or 1.0; 15–39 years: male-to-female ratio, 552/333 or 1.7, $P < 0.001$). During the period 1989–1995, around 5.5 million people aged 0–39 years resided in Belgium. Assuming that the IDDM incidence rate in Belgium equals that in the Antwerp district, we would expect that each year ~550 Belgian residents would develop IDDM (~200 new cases aged 0–14 years and ~350 new cases aged 15–39 years). Based on the yearly number of voluntary reported cases to the BDR (1,466/7 years or 209/year), the ascertainment rate for Belgium was ~40%.

Regarding the clinical characteristics of IDDM patients at diagnosis, the frequency of reported symptoms, such as polyuria and/or polydypsia and/or weight loss, did not differ according to age both in Antwerp (0–14 years: 118/125 [94%]; 15–39 years: 184/190 [97%], $P > 0.05$) and in Belgium (0–14 years: 449/474 [95%]; 15–39 years: 738/767 [96%], $P > 0.05$). However, young patients had a shorter duration of clinical symptoms than older patients both in Antwerp (median [range]: 3 [0–16] vs. 4 [0–100] weeks, $P = 0.007$) and in Belgium (median [range]: 3 [0–20] vs. 8 [0–260] weeks, $P < 0.001$). Ketonuria was more frequently reported in IDDM children under age 15 years (Antwerp: 112/123 [91%] vs. 128/186 [69%] thereafter, $P < 0.001$; Belgium: 368/426 [86%] vs. 488/645 [76%] thereafter, $P < 0.001$).

HLA-*DQ* genotypes could be determined in 80% (272/341) of the recruited Antwerp IDDM patients and in 94% (1,374/1,466) of the recruited Belgian IDDM patients (Table 3). The genotypes were subdivided in three groups according to the presence or absence of the *DQA1*0301-DQB1*0302* or *DQA1*0501-DQB1*0201* risk haplotype. The prevalence of the HLA-*DQ* genotypes varied according to age both in Antwerp and Belgium: IDDM children below age 15 years tended to carry the *DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201* high-risk genotype more frequently; conversely, genotypes without both HLA-*DQ* risk haplotypes were more common in patients above that age.

Both in Antwerp and Belgium, serum for the determination of autoantibodies could be sampled at clinical onset in at least 48% of the patients (Table 4). The prevalence of autoantibodies was strikingly age dependent. Both in Antwerp and Belgium, IAAs, ICAs, and IA-2-Abs decreased significantly with age, whereas GAD65-Abs tended to increase with age. More than 89% of the IDDM patients in Antwerp and Belgium were positive for at least one type of autoantibody. The simultaneous presence of four types of autoantibodies occurred more frequently in the youngest age-group, both in Antwerp and Belgium.

**Table 2—*Annual incidence rates (per 100,000) of IDDM by age and sex in the Antwerp district, 1989–1995***

| | Males | | Females | | Total | |
|---|---|---|---|---|---|---|
| Age (years) | Cases | Incidence rate (95% CI) | Cases | Incidence rate (95% CI) | Cases | Incidence rate (95% CI) |
| 0–4 | 11 | 5.5 (2.8–10.0) | 12 | 6.3 (3.2–11.0) | 23 | 5.9 (3.7–8.9) |
| 5–9 | 22 | 11.9 (7.5–17.8) | 24 | 12.4 (7.9–18.7) | 46 | 12.1 (8.9–16.2) |
| 10–14 | 29 | 15.2 (10.2–21.8) | 35 | 19.2 (13.4–26.7) | 64 | 17.1 (13.2–21.9) |
| 15–19 | 21 | 11.0 (6.8–16.8) | 17 | 9.2 (5.4–14.8) | 38 | 10.1 (7.2–13.9) |
| 20–24 | 18 | 7.9 (4.7–12.6) | 19 | 8.6 (5.2–13.5) | 37 | 8.3 (5.8–11.4) |
| 25–29 | 35 | 13.4 (9.4–18.7) | 16 | 6.4 (3.6–10.4) | 51 | 10.0 (7.4–13.1) |
| 30–34 | 32 | 12.2 (8.3–17.2) | 15 | 6.0 (3.3–9.9) | 47 | 9.2 (6.7–12.2) |
| 35–39 | 25 | 10.2 (6.6–15.1) | 10 | 4.3 (2.0–7.9) | 35 | 7.3 (5.1–10.2) |
| 0–14* | 62 | 10.7 (8.2–13.7) | 71 | 12.8 (10.0–16.2) | 133 | 11.8 (9.8–13.9) |
| 15–39* | 131 | 11.0 (9.2–13.0) | 77 | 6.9† (5.4–8.6) | 208 | 8.9 (7.8–10.2) |

*Age- and sex-standardized incidence rates for the age-groups 0–14 and 15–39 years. Poisson regression analysis (35): the total incidence rate varied significantly by 5-year age-groups ($P < 0.001$); †$P = 0.003$ vs. females 0–14 years and males 15–39 years.

Table 3—*Prevalence of HLA-DQ genotypes in IDDM patients in the Antwerp district and Belgium, 1989–1995*

| HLA-DQA1*-DQB1* genotype | Antwerp ($n$ = 272) 0–14 years | 15–39 years | $P$ | Belgium ($n$ = 1,374) 0–14 years | 15–39 years | $P$ |
|---|---|---|---|---|---|---|
| $n$ | 111 | 161 | | 543 | 831 | |
| 0301-0302/0501-0201 | 33 (30) | 33 (20) | 0.081 | 182 (34) | 184 (22) | <0.001 |
| 0301-0302 or 0501-0201 | 66 (60) | 85 (53) | >0.05 | 302 (56) | 480 (58) | >0.05 |
| Non(0301-0302)/non(0501-0201) | 12 (11) | 43 (27) | 0.002 | 59 (11) | 167 (20) | <0.001 |
| Overall $P$ | | | 0.004 | | | <0.001 |

Data are $n$ (%). Both for Antwerp and for Belgium, $P$ values ($\chi^2$ test) for testing the age dependency of the three genotypes were calculated, corrected for the number of comparisons ($n$ = 3) (Bonferroni), and considered significant if $P < 0.05/3$ or $P < 0.017$.

**CONCLUSIONS** — This study provides information on the epidemiology of IDDM in the Antwerp district for the age-group 0–39 years. Cases were ascertained prospectively through participants of the BDR and retrospectively through non-BDR pediatricians and endocrinologists via mail and telephone. The completeness of ascertainment, calculated by the capture-recapture method (34), was 98% in children aged 0–14 years and 85% in adults aged 15–39 years. The difference in ascertainment rate between pediatricians and endocrinologists could be due to the difference in referral rate of diabetic cases by general physicians to the specialists: children with newly diagnosed IDDM are more consistently referred to a specialist than adult newly diagnosed diabetic patients. Compared with the other European countries in the EURODIAB ACE study for the age-group 0–14 years (4), the Antwerp district is characterized by an intermediate rate (11.8/100,000). This rate is comparable with that in neighboring countries, such as the Netherlands (11.0/100,000) (4), Luxembourg (10.1/100,00) (4), and Germany (11.6/100,000) (36), lower than in the U.K. (16.4/100,000) (4), and higher than in France (7.8/100,000) (4). The incidence rate in the 0–14 years age-group was similar to that in the 15–39 years age-group (8.9/100,000). However, the larger size of the denominator population in the latter group determined that, in absolute numbers, the majority of new IDDM cases was adults aged 15–39 years (61%). This proportion is an underestimation considering the lower rate of ascertainment in this group (85%) and the noninclusion of the so-called LADA patients (latent autoimmune diabetes in adults), which is a subgroup of patients who are initially classified as having NIDDM but progressively develop insulin dependency (37). The present data indicate that the incidence rate of IDDM among adult diabetic patients is higher than previously expected. Meta-analysis of data from other regional and national diabetes registries studying the diabetic population above age 15 years (Denmark [8], Croatia [13], Italy [Turin (15,16), Pavia (22)], Sardinia [18], Spain [19], Poland [21]) has already revealed this notion. Although data are not yet available, it is conceivable that a comparable number of IDDM patients become clinically overt above the age of 40 years. It thus becomes increasingly clear that the pathogenesis of IDDM should not be restricted to the period of childhood. Juvenile-onset cases (which, so far, have been the subject of most clinical studies of IDDM) cannot be considered a characteristic of the disease. They rather represent one form with more severe and early clinical symptoms. Adult-onset cases require a more systematic study to identify the biological basis and the genetic and environmental reasons for the later development of clinical symptoms.

Both sexes had a similar incidence rate of IDDM before age 15 years. However, in the age-group 15–39 years, the incidence rates decrease with age in females older than age 15, but not in males, resulting in twofold higher incidence rate in males than in females. This sex-dependent difference in risk in older age-groups has also been observed in other countries with an intermediate or high risk (Croatia [13], Italy [Turin {16}], Norway [17], Sardinia [18], Spain [19], Sweden [23], Denmark [14]), but not in regions with a low risk (Barbados [20], Poland [21], Pavia [22]). It may be caused by the effect of sex hormones as well as by lifestyle factors, such as obesity, physical activity, and diet, as recently shown for NIDDM (38). Finally, it should be noted that one of the putative IDDM susceptibility loci (*DXS1068*) has been mapped to the X-chromosome (39), suggesting a role for sex-linked genetic factors in the pathogen-

Table 4—*Prevalence of autoantibodies in recent-onset IDDM patients in the Antwerp district and Belgium, 1989–1995*

| Autoantibodies | Antwerp 0–14 years | 15–39 years | $P$ | Belgium 0–14 years | 15–39 years | $P$ |
|---|---|---|---|---|---|---|
| IAAs | 54/84 (64) | 40/121 (33) | <0.001 | 200/320 (62) | 184/527 (35) | <0.001 |
| ICAs | 75/84 (89) | 81/121 (67) | <0.001 | 265/320 (83) | 349/527 (66) | <0.001 |
| GAD65-Abs | 49/71 (69) | 89/106 (84) | <0.02 | 210/281 (75) | 379/471 (80) | >0.05 |
| IA-2-Abs | 54/67 (81) | 48/97 (49) | <0.001 | 189/263 (72) | 203/428 (47) | <0.001 |
| ≥1 type of autoantibody | 65/67 (97) | 90/97 (93) | >0.05 | 254/263 (97) | 380/428 (89) | <0.001 |
| 4 types of autoantibodies | 27/67 (40) | 20/97 (21) | 0.006 | 95/263 (36) | 80/428 (19) | <0.001 |

Data are $n$ (%). Both for Antwerp and for Belgium, $P$ values ($\chi^2$ test) for testing the age dependency of the autoantibody prevalence, alone or in combination, were calculated, corrected for the number of comparisons ($n$ = 6) (Bonferroni), and considered significant if $P < 0.05/6$ or $P < 0.008$.

esis of the disease. Comparison of data collected from a high ascertainment (92%) subregion (Antwerp district: 9% of the Belgian population) with those from the lower ascertainment (40%) region (Belgium) indicates similar findings. The Belgian cases also exhibit a male-to-female ratio of 1.0 in the age-group 0–14 years and of 1.7 in the 15–39 years age-group.

No significant differences were observed in frequency of symptoms. Both in Antwerp and Belgium, adults presented a longer duration of symptoms and a lower prevalence of ketonuria than children, as also reported elsewhere (12); there was no difference in the biological data obtained in the Antwerp district and Belgium. In both groups, the prevalence of genetic and immunological markers varied significantly with age at onset. The HLA-*DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201* high-risk genotype, IAAs, ICAs, and IA-2-Abs occurred more frequently in children than in adults, whereas GAD65-Abs were more prevalent in adults than in children. These data are consistent with previous reports (6,10,12,30,32,40–43). On the other hand, ~90% or more of the children and adults showed at least one IDDM-specific autoantibody in agreement with previous work from our group and others (28,43,44). It is therefore unlikely that misclassified NIDDM patients were included in the adult group.

In conclusion, the incidence rate of IDDM in the West European Antwerp district is comparable in the 0–14 and 15–39 years age-groups. In the 0–14 years age-group, the rate is intermediate when compared with that in other European countries. In absolute numbers, >60% of new cases are diagnosed in adulthood. Incidence rates decrease with age in females older than age 15 years but not in males. Comparison of data collected from the high-ascertainment (92%) Antwerp district with those from the lower-ascertainment (40%) region covering the whole of Belgium does not identify differences in population composition, clinical presentation, and biological characteristics. The data collected nationwide by the BDR are thus considered representative for the total Belgian population and form a reliable basis for the study of genetic, immunological, and environmental determinants in the development of IDDM. The larger number of cases available from a nationwide recruitment offer a considerable advantage for undertaking such study.

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