Residual β-Cell Function and Male/Female Ratio Are Higher in Incident Young Adults Than in Children

The registry of type 1 diabetes of the province of Turin, Italy, 1984–2000

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OBJECTIVE — The hypothesis of age-dependent variations in epidemiologic and clinical features at onset of type 1 diabetes has been assessed in the registry of the province of Turin, Italy.

RESEARCH DESIGN AND METHODS — The study base is the population 0–29 years of age of the province of Turin, in the period from 1984 to 2000. Islet cell antibody (ICA), GAD antibody (GADA), antibodies to protein tyrosine phosphatase (IA2), and C-peptide were measured in subgroups of the cohort.

RESULTS — One thousand fifty-six incident cases have been identified (completeness of ascertainment 98.1%). Rates per 100,000 person-years were similar in males and females in the age-group 0–14 years (10.7, 95% CI 9.5–12.0 vs. 9.8, 8.6–11.1). In the age-group 15–29 years, males had higher risk than females (7.7, 6.9–8.6 vs. 5.3, 4.6–6.1; rate ratio, 1.46, 95% CI 1.23–1.74; $P = 0.00002$). Fasting plasma C-peptide values ($n = 575$) were twofold lower in the age-group 0–14 years than in the age-group 15–29 years (0.10 vs. 0.23 nmol/l; $P < 0.0001$). Frequencies of ICA and IA2 positivities ($n = 183$) decreased with increasing age, whereas frequency of GADA positivity increased. Idiopathic cases were 12.6% and had higher mean values of fasting (0.28 vs. 0.14 nmol/l; $P = 0.043$) and stimulated C-peptide (0.59 vs. 0.34 nmol/l; $P = 0.05$). In logistic regression analyses, subjects with fasting C-peptide values in the upper quartile had higher likelihood of being older (odds ratio 1.20 for year, 95% CI 1.11–1.28), ICA negative (0.26, 0.10–0.70), and female (1.29, 0.48–3.42).

CONCLUSIONS — This study shows *1*) sex differences in incidence rates in young adults; *2*) better preserved β-cell function in young adults, in idiopathic cases (12%), and in ICA-negative cases; and *3*) lower frequencies of ICA and IA2 positivities and higher frequency of GADA positivity in young adults than in children.

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Abbreviations: GADA, GAD antibody; IA2, antibodies to protein tyrosine phosphatase; ICA, islet cell antibody.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Epidemiologic studies extending the recruitment of cases up to adults have provided evidence that the incidence of type 1 diabetes in postpubertal age is higher than previously hypothesized (1–4). Immunologic heterogeneity by age at onset, with higher frequencies of multiple markers of β-cell autoimmunity in children than in adults, has also been shown, suggesting that diabetes in adults could be mainly a slowly progressive disease, with lower reduction of insulin production than in younger patients (5,6). Indeed, the Diabetes Control and Complications Trial study showed that a higher proportion of adults than adolescents with duration of diabetes >5 years retained residual β-cell function, assessed through basal and stimulated C-peptide levels (7). This finding is relevant, because better glycemic control and lower risk for hypoglycemia and chronic complications have also been found in patients with stimulated C-peptide values >0.20 pmol/ml (8). Few studies, however, have assessed β-cell function at diabetes onset, and all but one of them have been conducted in clinic-based rather than in population-based cohorts, so that selection bias in results cannot be ruled out (9–14).

The registry of type 1 diabetes of the province of Turin has been recruiting incidence cases in the age group 0–29 years since 1984, providing the first epidemiologic data of the disease in Italy (15,16). This report extends previous observations over a 17-year period, allowing to provide more accurate estimates of risk both in children (0–14 years) and young adults (15–29 years). Moreover, the present study tests the hypothesis that variations in residual β-cell function and in clinical and immunologic features at diabetes onset are age dependent.

RESEARCH DESIGN AND METHODS

— The study base of this report is the resident population 0–29

Table 1—*Age- and sex-specific incidence rate/100,000 person-years of type 1 diabetes in the province of Turin, Italy, from 1984 to 2000*

	Males (n = 603)		Females (n = 453)		Total (n = 1,056)	
Age-group (years)	No. of cases	Rates/100,000	No. of cases	Rates/100,000	No. of cases	Rates/100,000
0–4	53	6.5 (4.9–8.6)	52	7.0 (5.3–9.2)	105	6.8 (5.6–8.2)
5–9	92	10.9 (8.9–13.4)	88	11.0 (8.9–13.6)	180	11.0 (9.5–12.7)
10–14	136	13.6 (11.5–16.1)	104	10.9 (9.0–13.2)	240	12.3 (10.8–13.9)
15–19	108	8.9 (7.3–10.7)	74	6.4 (5.1–8.0)	182	7.7 (6.6–8.9)
20–24	115	7.9 (6.6–9.5)	72	5.3 (4.2–6.6)	187	6.6 (5.7–7.6)
25–29	99	6.6 (5.4–8.1)	63	4.4 (3.4–5.6)	162	5.5 (4.7–6.5)
0–14	281	10.7 (9.5–12.0)	244	9.8 (8.6–11.1)	525	10.2 (9.4–11.2)
15–29	322	7.7 (6.9–8.6)	209	5.3 (4.6–6.1)	531	6.5 (6.0–7.1)

years of age of the province of Turin, Italy, in the period from 1 January 1984 to 31 December 2000. Incident cases of type 1 diabetes arising during the study period were identified through the following sources of ascertainment: *1*) diabetes clinics where diabetic patients are referred after diagnosis (primary source); *2*) files of hospital discharges from the public and private hospitals in the province of Turin (secondary source in period 1984–1993); and *3*) files of all subjects who obtained exemption from payment of drugs, syringes, and glucose-monitoring strips due to a diagnosis of diabetes (secondary source in period 1994–2000) (15–17).

Clinical charts were reviewed to assess clinical features at diabetes onset (glycemia, ketonuria, and hospital admission). In the period 1997–2000, diabetologists were periodically contacted by the coordinating center to identify incident cases within 2 months from diagnosis, in order to perform centralized measurements of markers of β-cell autoimmunity and stimulated C-peptide values (6 min after an intravenous injection of 1 mg of glucagon). Main causes of nonrecruitment were absence of notification by 2 months from diagnosis, inadequate quantity of blood sample, and absence of informed consent.

β-Cell function was estimated by centralized plasma C-peptide measurements (DPC, Los Angeles, CA; normal values 0.36–1.17 nmol/l). GAD antibody (GADA) and antibodies to protein tyrosine phosphatase (IA2) were measured by a radioligand assay using human recombinant antigens (Medipan Diagnostica, Selchow, Germany); immunocomplexes were precipitated with protein A according to the method of Schmidli (18). GADA values >0.9 units/ml and IA2 values >0.75 units/ml were considered positive. Sensitivity and specificity were 84 and 93% for GADA and 60 and 100% for IA2, respectively, at the first proficiency evaluation of the Diabetes Antibody Standardization Program (laboratory identification 124) (18).

Islet cell antibodies (ICAs) were assayed by indirect immunofluorescence on frozen sections of human blood group 0 pancreas with fluorescein isothiocyanate–conjugated rabbit antibodies. ICA positivity was expressed in Juvenile Diabetes Foundation units (JDF units) by a standard curve based on the international JDF units reference sera sample. An ICA ≥5 JDF units was considered positive. Sensitivity and specificity were 100% at the third ICA proficiency program of the Research Institute for Children, New Orleans, Louisiana (laboratory identification 13).

Statistical analyses

Denominators of incidence rates were intercensual estimates of residents in the province of Turin, Italy. The two-sample capture-recapture method was employed to estimate completeness of ascertainment (17). C-peptide values were nonnormally distributed and were analyzed after logarithmic transformation. Differences in clinical characteristics of incident cases between age-groups 0–14 and 15–29 years were assessed using the Student's t test for continuous variables and χ^2 test for ordinal variables; results are shown as means (±SD) and geometric means for normally and nonnormally distributed variables, respectively. Linear regression analyses were performed to assess whether C-peptide values were linearly associated with age and plasma glucose at onset (Table 2). The χ^2 test was employed to determine whether distributions of cases by age-groups (Table 2) or quartiles of fasting C-peptide (Table 3) were significantly different from that expected by chance. ANCOVA was employed to compare peptide values adjusted for age among subjects positive and negative for ICA, GADA, and IA2 (Table 4).

Logistic regression analysis was then performed to assess variables independently associated with upper quartile values of fasting C-peptide (reference, first quartile). The likelihood ratio test was used to test the significance of variables. All analyses were performed using Stata (Stata Release 8.0; Stata, College Station, TX). P values <0.05 were considered statistically significant.

RESULTS — In the period from 1984 to 2000, 1,056 incident cases of type 1 diabetes aged 0–29 years have been identified in the province of Turin, 1,042 through the primary source, 899 through the secondary source, and 793 through both the primary and secondary sources, giving an estimated completeness of ascertainment of 98.1% (99.1% in the age-group 0–14 years and 96.7% in the age-group 15–29 years). During the study period, no temporal variations in completeness of ascertainment were found.

Table 1 shows similar rates in the age-groups 5–9 years and 10–14 years in females, whereas in males there was a tendency toward a peak in the age-group 10–14 years, although with slight overlapping of CIs. Similar rates in males and females were evident in the age-group 0–14 years, whereas in the age-group 15–29 years, rates were significantly higher in males: rate ratio 1.46 (95% CI 1.23–1.74; P = 0.00002)

Table 2 shows negative trends by age at onset in mean fasting plasma glucose and in frequencies of ketonuria and hos-

Table 2—*Clinical, metabolic, and immunological features at diabetes onset in the population-based cohort of incident cases of type 1 diabetes in the province of Turin, Italy, from 1984 to 2000*

Age-group (years)	Glucose (mmol/l)	Ketonuria	Hospital admission	Fasting C-peptide (nmol/l)	Stimulated C-peptide (nmol/l)	ICA+	GADA+	IA2+
n	842	769	947	575	180	262	254	183
0–4	24.9 ± 8.3	90 (96.8)	102 (99.0)	0.07	0.14	11 (64.7)	10 (58.8)	8 (66.7)
5–9	22.9 ± 11.3	146 (90.7)	174 (98.9)	0.08	0.19	33 (64.7)	30 (58.82)	31 (81.6)
10–14	21.9 ± 8.6	179 (93.7)	200 (88.5)	0.15	0.27	28 (59.6)	26 (54.2)	21 (65.6)
15–19	24.1 ± 10.7	95 (88.0)	114 (74.5)	0.21	0.48	23 (53.5)	27 (64.3)	11 (44.0)
20–24	23.4 ± 10.6	96 (90.6)	94 (61.4)	0.23	0.48	30 (47.6)	41 (71.9)	18 (51.4)
25–29	21.1 ± 10.2	93 (84.6)	83 (61.0)	0.24	0.43	19 (46.3)	26 (66.7)	10 (50.0)
P	0.04*	0.03	<0.0001	<0.0001*	<0.0001*	0.34	0.50	0.003
0–14	22.9 ± 9.6	415 (93.3)	476 (94.3)	0.10	0.21	72 (62.6)	66 (56.9)	60 (73.2)
15–29	22.8 ± 10.6	284 (87.6)	291 (65.8)	0.23	0.47	72 (49.0)	94 (68.1)	39 (48.7)
P	0.89†	0.008	<0.0001	<0.0001†	<0.001†	0.028	0.06	0.001

Data are means ± SD, geometric means, or *n* (%). *Based on linear regression analysis; †based on Student's *t* test.

pital admission at diagnosis. In 575 of 1,056 (54.4%) incident cases, centralized measurements of fasting plasma C-peptide were available for analyses; they were 355 of 525 (67.6%) cases aged 0–14 years and 219 of 531 (41.4%) cases aged 15–29 years. Mean age at onset of the disease was therefore lower in examined subjects than in nonexamined ones (14.0 ± 7.8 vs. 17.8 ± 7.4 years; $P < 0.001$. Mean fasting plasma C-peptide values were almost twofold higher in young adults than in children. Indeed, age and fasting C-peptide values were linearly associated ($\beta = 0.06$; $P < 0.0001$). This positive relationship was also evident comparing the distributions of fasting C-peptide quartiles in children and young adults (Table 3). Similar values, however, were found in males and females, irrespective of age (0.14 and 0.13 nmol/l, respectively).

Stimulated C-peptide values were measured in 180 of 288 (62%) incident cases in the period 1997–2000. With respect to nonrecruited subjects, however, no significant differences in age at onset were found. Basal and stimulated values were highly correlated ($r = 0.82$; $P < 0.0001$). Similarly, therefore, stimulated C-peptide values were linearly associated with age at onset of the disease (Table 2).

ICA and GADA were measured in 262 of 288 (91%) incident cases in the period 1997–2000, whereas in 183 of them IA2 measurements were also available. Heterogeneities by age at onset in the distributions of markers of β-cell autoimmunity were found (Table 2); whereas frequencies of ICA and IA2 positivities decreased with increasing age at onset, an increasing trend in frequencies of GADA positivity across age-groups was found. No sex differences in positivities of GADA (55.1% in males, 44.9% in females; $P = 0.33$) or IA2 (61.1% and 62.9%; $P = 0.82$) were found, whereas frequency of ICA positivity in males was higher than in females (51.3% and 48.6%, respectively; $P = 0.05$).

Figure 1 shows distributions of ICA, GADA, and IA2 positivities by age at onset in 183 incident cases without missing values. Of them, 23 (12.6%) had no markers of β-cell autoimmunity and were defined as idiopathic (10 of 82 in age-group 0–14 years and 12 of 79 in age-group 15–29 years). With respect to subjects with at least one marker positivity, they had higher values of fasting C-peptide (0.28 vs. 0.14 nmol/l; $P = 0.043$) and stimulated C-peptide (0.59 vs. 0.34 nmol/l; $P = 0.05$). Frequencies of subjects with positivities for one, two, and three markers were 20.7, 28.0, and 39.0% in the age-group 0–14 years and 25.3, 32.9, and 26.6% in the age-group 15–29 years, respectively ($P = 0.42$).

ICA-positive subjects had lower residual β-cell function than ICA-negative subjects (fasting C-peptide: 0.12 vs. 0.19 nmol/l, $P = 0.036$; stimulated C-peptide: 0.28 vs. 0.43 nmol/l, $P = 0.005$), whereas no differences were found between GADA- or IA2-positive and -negative subjects. As shown in Table 4, differences in point estimates of C-peptide between ICA-positive and -negative subjects persisted even after age adjustment, although with slightly overlapping of CIs.

In logistic regression analyses, compared with incident cases with fasting C-peptide values in the lower quartile, cases with values in the upper quartile had higher likelihood of being older (odds ratio 1.20 for year, 95% CI 1.11–1.28), ICA negative (0.26, 0.10–0.70), and female, although not significantly (1.29, 0.48–3.42). GADA and IA2 positivities did not add significantly to the model. The protective role of ICA negativity was evident even in subgroup analysis; indeed, odds ratios in the age-groups 0–14 and 15–29

Table 3—*Quartiles of fasting C-peptide levels, by age at onset of diabetes, in incident cases of type 1 diabetes in the province of Turin, Italy, from 1984 to 2000*

Age at onset (years)	Fasting C-peptide (nmol/l)			
	<0.08	0.08–0.16	0.17–0.31	>0.31
0–14	123 (34.7)	108 (30.4)	69 (19.4)	55 (15.5)
15–29	22 (10.0)	37 (16.9)	72 (32.9)	88 (40.2)

Data are *n* (%). $P < 0.0001$.

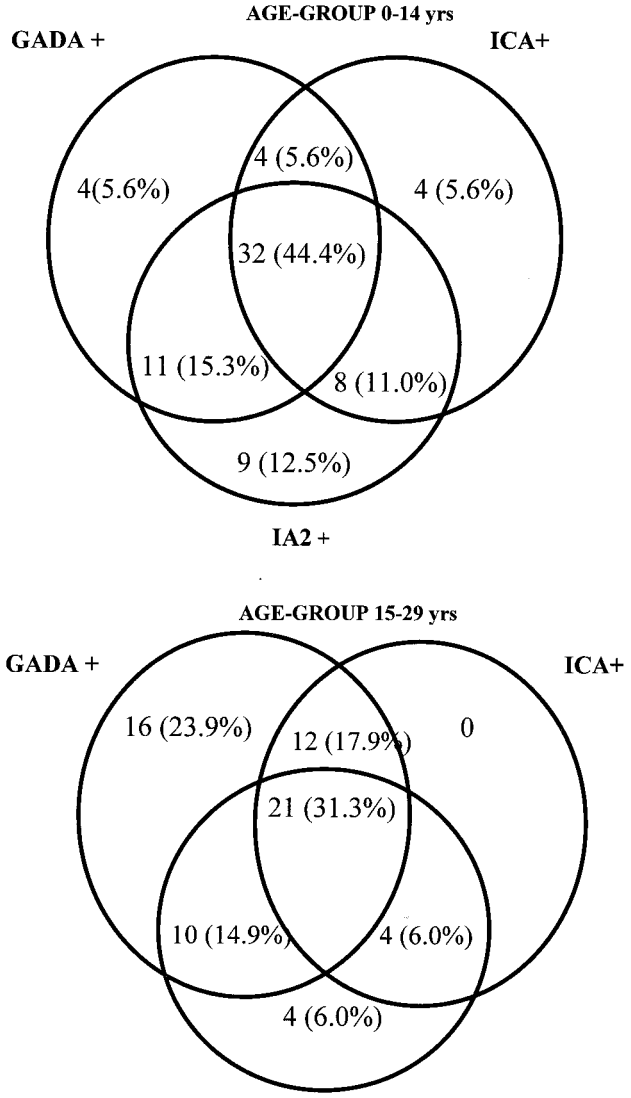

Figure 1—*Distributions of markers of β-cell autoimmunity in a subgroup of 183 incident cases of type 1 diabetes in the registry of the province of Turin, Italy, by age-groups 0–14 and 15–29 years. Frequencies refer to subjects with at least one marker positivity.*

years were 0.39 (0.12–1.28) and 0.21 (0.04–1.14), respectively.

CONCLUSIONS— This study shows heterogeneity of type 1 diabetes by age at onset, with both better preserved β-cell function and higher male/female incidence ratio in young adults than in children. These findings were obtained in a population-based registry and their validity assured by high estimated completeness of ascertainment in both children and young adults and by a large proportion (54%) of subjects with fasting C-peptide levels measured in a centralized laboratory.

Our finding of better preserved β-cell function at onset of type 1 diabetes in young adults than in children is consistent with results of the Diabetes Control and Complications Trial study in subjects with duration of diabetes >5 years (7,8). The Belgian Registry only provided similar findings at diabetes onset in a cohort of 172 patients <40 years of age (6), whereas a Finnish clinic-based study found no differences in fasting C-peptide values between 252 subjects aged <20 years and 100 subjects aged >20 years (5). Recently, a 52% lower response of plasma C-peptide to the mixed meal Sustacal has been found in 41 young adults with new-onset diabetes than in control subjects (20). Altogether, these findings strengthen the hypothesis of clinical heterogeneity of the disease by age at onset and would have implications in the recruitment of patients for intervention trials having as the main outcome the preservation of residual β-cell function (21). Whereas these differences are due to etiopathogenetic heterogeneity by age at onset, with different determinants in the youngest age-groups and in the oldest ones, it is unknown.

Sex differences in incidence of type 1 diabetes in young adults, with higher risk in males than in females, were first pointed out in a report of our registry limited to 298 incident cases in the period 1984–1988 (15) and later were confirmed by the few registries extending the recruitment of subjects at least up to 29 years (1–4). At present, no explanation for this finding has been provided, although hormonal-linked factors are likely to be involved (1).

The present study is based on 1,056

Table 4—*Age-adjusted fasting and stimulated C-peptide levels, by markers of β-cell autoimmunity, in incident cases of type 1 diabetes in the province of Turin, Italy, from 1984 to 2000*

	Fasting C-peptide [nmol/l (95% CI)]	Stimulated C-peptide [nmol/l (95% CI)]
ICA−	0.13 (0.10–0.16)	0.43 (0.35–0.52)
ICA+	0.10 (0.15–0.26)	0.27 (0.22–0.32)
P	0.14	0.01
GADA−	0.17 (0.13–0.22)	0.31 (0.24–0.40)
GADA+	0.15 (0.12–0.18)	0.34 (0.28–0.40)
P	0.17	0.91
IA2−	0.20 (0.14–0.29)	0.42 (0.32–0.54)
IA2+	0.13 (0.10–0.18)	0.32 (0.25–0.41)
P	0.43	0.42

incident cases recruited over a 17-year study period, with 98% estimated completeness of ascertainment. This report, therefore, allows to provide accurate estimates of rates, as confirmed by the narrow CIs surrounding estimates, and indicates that risk for type 1 diabetes in young adults in Italy, although lower than in childhood, is not negligible. Most registries limit recruitment of incident cases up to age 14 years, given the low completeness of ascertainment generally obtained in postpubertal ages. At present, therefore, it cannot be excluded that the hypothesis that geographic differences in incidence of the disease would be merely related to differences in age at onset, with persisting high risk and slower rates of progression after puberty in areas at medium risk for childhood-onset diabetes than in areas at high risk. Considering that the majority of subjects with the disease arise in adults, registries should extend recruitment of cases at least up to 30 years, thus allowing also to disentangle temporal trends in incidence rates by age, period, and cohort (3,16).

The present report provides evidence that compared with ICA-negative subjects, ICA-positive subjects have lower residual β-cell function at the onset of the disease, independent of age and sex, whereas GADA and IA2 positivities are not significantly associated with β-cell function. These findings are consistent with a Finnish study showing lower residual β-cell function at the onset of the disease in children ICA and IAA positive than in those negative (10). Even in that study, no differences were found between GADA-positive and -negative patients.

Idiopathic type 1 diabetes has been suggested to be a clinically distinct type of diabetes, probably a heterogeneous, non–autoimmune-mediated, insulin-deficient form of diabetes, described mainly in African Americans (22). In this cohort, frequencies of subjects testing negative to all markers were similarly high in children and young adults (12%). Moreover, incident cases with idiopathic type 1 diabetes were characterized by higher β-cell function than subjects with at least one marker positivity.

Heterogeneity by sex in prevalence of markers of β-cell autoimmunity in adolescents, with prevailing IAA in males and GADA in females, has been recently described (23). In our study, frequency of ICA positivity was significantly higher in males than in females, even if based on small numbers of tested cases.

In conclusion, this study shows *1*) sex differences in incidence rates of type 1 diabetes in young adults, with higher risk in males than in females; *2*) better preserved β-cell function in young adults than in children, in idiopathic cases (12%), and in ICA-negative cases; and *3*) lower frequencies of ICA and IA2 positivities and higher frequency of GADA positivity in young adults than in children.

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APPENDIX

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