Ethnic Differences in the Incidence of Childhood IDDM in Israel (1965–1993)

Marked increase since 1985, especially in Yemenite Jews

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OBJECTIVE — To establish the changes in the incidence of childhood IDDM during the years 1965–1993 in the different ethnic groups in Israel.

RESEARCH DESIGN AND METHODS — A whole-country register of childhood IDDM (0–17 years) was started in Israel in 1965. Onset of IDDM was considered to be the date of first insulin injection. The data were collected from all outpatient clinics and hospitals. Ascertainment is estimated to be over 95%.

RESULTS — A total of 1,868 patients were registered for a period of 28 years. Marked differences were found between ethnic groups. The highest incidence was among the Yemenite Jews, who reached an incidence of 18.5/10^5, followed by Ashkenazi Jews (10.0/10^5), non-Ashkenazi Jews, except Yemenites (7.3/10^5), and Arabs (2.9/10^5). In addition, it was found that in all Jewish subgroups, in contrast with the Arabs, there was a marked increase in incidence after 1985.

CONCLUSIONS — Israel is a country with low, intermediate, and high incidence of childhood IDDM. The interethnic differences in incidence are probably due to genetic factors. However, the significant increase in incidence since 1985 in the Jewish population is ascribed to thus far unidentified environmental factors. It is hypothesized that the marked increase in IDDM is due to environmental factors linked to changes in affluence and lifestyle. These may also explain the difference in incidence between the Jewish and Arab populations, the latter living more in rural areas and leading a more traditional lifestyle.

The initiation of international epidemiology studies such as Diabetes Epidemiology Research International (DERI) (1,2), Eurodiab Aetiology of Childhood Diabetes on an Epidemiological Basis (ACE) (3), and World Health Organization Diabetes Mondial (WHO DIAMOND) (4) has stimulated the establishment of many country- or region-wide IDDM registries. These studies have shown that there is a wide variation in the incidence in different populations, the highest incidence being in Finland and Sardinia, and the lowest in the Far East (1–5). One of the first countries to establish a registry was Israel (4) with a low incidence (6–9) compared with most European countries (3) and the U.S. (2). In recent years the incidence of IDDM in childhood and adolescence appears to be increasing in many countries of the world: in Europe (10–17), in the U.S. (18), as well as in the Arab peninsula (19) and the Far East (20,21). With the exception of the Austrian survey (17), all the studies covered a few years only.

In the following article, we describe the incidence of childhood IDDM (0–17 years) in Israel from 1965 to 1993, the longest known whole-country study so far. We shall demonstrate differences in incidence of IDDM between various ethnic groups ranging from low to high and a recent dramatic increase in incidence in the Jewish population, especially those of Yemenite origin as compared with Arabs.

RESEARCH DESIGN AND METHODS

Subjects and methods

Since 1965, our group is in charge of the epidemiology of childhood IDDM (all children ages 0–17 years) in Israel. The first period, 1965–1979, was within the frame of the DERI study, coordinated in Pittsburgh (U.S.) (1), and subsequently we joined the Eurodiab ACE study group, coordinated in Odense (Denmark) (2).

Starting 1 January 1965, we established a whole-country registry for childhood and puberty-onset IDDM. The criteria for inclusion were those newly diagnosed IDDM patients, who were permanent residents of Israel, below age 18 at the time of their first insulin injection, and requiring continuous insulin treatment.

Patients with secondary diabetes (e.g., due to thalassemia major, cystic fibrosis, pancreatectomy, or corticosteroids) were excluded. The date of onset of IDDM was considered to be the day of the patient's first insulin injection.

To achieve complete ascertainment and verification of the diagnosis and registry since 1965, the present investigators (I.S., O.G., Y.A.) reviewed all recorded admissions to hospitals in Israel and the medical files of all the diabetes and endocrinology outpatient clinics (including private) to which juveniles with diabetes are being referred. Further validation of the obtained registry was obtained by checking the lists of IDDM patients of the various Medical Insurance Organizations, the computer center of the Government Hospitals, the Army Recruiting Office, and the Registry of the Juvenile Diabetes Foundation of Israel. The completeness of ascertainment of the screening as estimated by the "capture-recapture" method (22) was over 95%.

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ACE, Aetiology of Childhood Diabetes on an Epidemiological Basis; DERI, Diabetes Epidemiology Research International.

Table 1—*Mean 5-year incidence and number of Jewish children and adolescents <18 years of age, with IDDM 1965–1993*

	1965–1969	1970–1974	1975–1979	1980–1984	1985–1989	1990–1993
Boys						
Incidence	3.2 (2.5–4.0)	4.2 (3.4–5.0)	4.4 (3.7–5.2)	4.1 (3.3–4.8)	6.2 (5.3–7.1)	7.0 (6.1–8.0)
n	74	104	124	123	199	201
Girls						
Incidence	3.1 (2.4–3.9)	4.5 (3.7–5.4)	5.0 (4.2–5.9)	4.9 (4.1–5.7)	6.0 (5.2–6.9)	7.6 (6.6–8.7)
n	68	107	134	141	184	206
Total incidence	3.2 (2.7–3.7)	4.3 (3.8–4.9)	4.7 (4.2–5.3)	4.5 (3.9–5.0)	6.1 (5.5–6.7)	7.3 (6.6–8.0)
n	142	211	258	264	383	407
Male/female ratio	1.03	0.92	0.88	0.84	1.03	0.9

Data are *n*/100,000 person-years (95% CI). *n* = 1,665.

Collection of data

Primary ascertainment was made from records of all pediatric and diabetic clinics to which children and adolescents with diabetes were referred, registries of all sick-funds, and lists of participants in diabetes camps. The records between 1965 and 1979 were reviewed by Bauman et al. (6).

Between 1965 and 1979 the study was retrospective, and starting from January 1980 the study was prospective. Twenty-eight clinics were identified in Israel as referral centers for children and adolescents with IDDM. A form was sent monthly to these clinics to be completed by the physician or nurse providing the following information for each child: name, surname, identity number, date of birth, sex, ethnic origin, date of first insulin administration, medical background, other diseases of patient and first relatives, hospital at which the diagnosis of IDDM was made, and name of hospital or outpatient clinic where follow-up took place. Every 2–3 months, one of the investigators visited each clinic to review the data collected. Our clinic treated ~60–70% of all juveniles with IDDM between 1965 and 1979 and 45–50% thereafter.

The general population data for each year were obtained from the Annual Publication of the Israel Central Bureau of Statistics. This publication provides information on the total number of individuals by age, sex, and parental country of birth.

The Israeli population includes two major population groups: Jews and Arabs. Among the Jews, by country of origin, are several ethnic subgroups: Ashkenazi Jews (originating from Europe, America, South Africa), non-Ashkenazi Jews (originating from North Africa and Asia, including the Yemenite Jews from the south of the Arab peninsula). Israeli Jews are those of Israeli-born fathers, and as the child is often an offspring of an inter-Jewish ethnic marriage, they are considered a mixed group.

Statistical analysis

Incidence rates were calculated as the number of newly diagnosed diabetic subjects per 100,000 person-years, in each of the groups formed by different values of sex, age, ethnic origin, and time-period. We used four age-groups: 0–4 years, 5–9 years, 10–14 years, and 15–17 years. Analysis was made using 5-year periods. As the validation for ethnic origin was considered incomplete for the period 1965–1979, subdivision into ethnic groups was made only for the period 1980–1993.

The 95% CIs were calculated on the basis of binomial distribution and the Poisson distribution, yielding identical results. For the overall estimate of influence of each of the independent variables on the incidence rate we used the logistic regression model (23), which yields virtually the same parameter estimates as a Poisson regression model (24).

RESULTS — Between 1 January 1965 and 31 December 1993, 1,868 subjects with juvenile-onset IDDM aged <18 years were registered. There were 922 boys and 946 girls. Table 1 presents the mean 5-year annual incidence of IDDM and 95% CIs in the Jewish population in Israel between 1965 and 1993 (*n* = 1,665). It shows that after a relatively stable period, 1970–1984, a progressive increase in incidence rates was registered. From 1990 to 1993 the incidence was more than doubled compared with 1965–1969. The trends and the values were similar for both sexes. Figure 1 shows the fluctuations in annual incidence rates for the same period, and the 5-year annual means.

Table 2 presents the 5-year annual mean incidence according to ethnic groups for

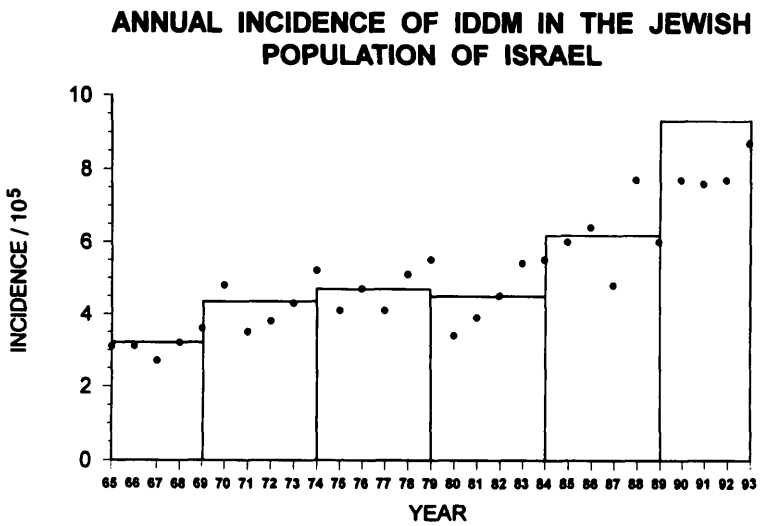

Figure 1—*Five-year annual means and yearly fluctuations of the incidence of IDDM in the Jewish population of Israel, 1965–1993.*

Table 2—*Five-year annual means in the incidence of IDDM in different ethnic groups in Israel, 1980–1993*

Group	1980–1984	1985–1989	1990–1993
Ashkenazi Jews	6.3 (5.0–7.6)	8.8 (7.2–10.4)	10.0 (8.3–11.7)
n	87	115	131
Non-Ashkenazi Jews*	3.6 (2.8–4.4)	5.3 (4.3–6.3)	7.3 (5.9–8.7)
n	82	111	106
Yemenite Jews	9.1 (5.1–13.1)	17.4 (11.0–23.9)	18.5 (9.4–27.5)
n	20	28	16
Israeli Jews†	3.7 (2.8–4.5)	4.8 (3:9–5.6)	5.7 (4.8–6.5)
n	75	129	154
Arabs	2.3 (1.6–3.0)	3.2 (2.4–4.0)	2.9 (2.1–3.8)
n	43	63	51
Undefined Jews‡	6.0	4.0	29

Data are mean (95% CI). Total means = 10^5; total *n* = 1,250. *Excludes Yemenite Jews. †Mixed Jewish ethnic group. ‡Probably Israeli Jews.

1980–1993. Two main findings are apparent. The first shows a significant difference in incidence of IDDM between the ethnic groups. Comparison of the incidence for 1980–1984 shows that the highest rates were found among the Yemenite Jews ($9.1/10^5$), followed by the Ashkenazi Jews ($6.3/10^5$). The remaining non-Ashkenazi Jews had a mean incidence of $3.6/10^5$, which was identical to the mixed-group of Israeli Jews ($3.7/10^5$). The lowest incidence was registered in the Israeli Arab population ($2.3/10^5$). The second finding is that in the Jewish population a marked increase in incidence was registered after 1985, whereas the Arab population showed little change.

Table 3 presents the incidence rate according to age-group and ethnic group for 1980–1993. The distribution between the sexes was equal. In the period 1980–1984 there was little difference in the incidence of IDDM between the ethnic groups in the youngest age-group (0–4), but there was a disproportionate incidence mainly after age 10. Starting with 1985, there was a marked (almost doubling) incidence in all age-groups of the Jewish population, but little change in the Arab population.

When calculating the incidence rate by age-group separately for the Yemenite Jews, we registered for the period 1988–1993 an incidence of $5.0/10^5$ for the age-group 0–5 years and $17.4/10^5$ for the pubertal age-group.

To estimate the determining factors in the IDDM incidence rates registered, a logistic regression analysis was used (Table 4). This analysis proves the significant dependence of the incidence rates on the age-groups, time-period, and ethnic origin.

Analysis of seasonality of onset revealed, despite some variability between years, the typical pattern of a higher incidence in the winter and lower in the summer months. This was true for all ethnic groups.

CONCLUSIONS — The present study, the longest whole-country childhood IDDM report, revealed information of great interest. There are two major findings: *1*) the very high incidence of IDDM in the Yemenite Jews, and 2) the marked increase in the incidence of IDDM in the Jewish population as compared with the Arabs. The high awareness of IDDM among the lay people and the health professionals in our country due to long-standing education programs, excludes the possibility that the increased incidence is due to increased detection and reporting.

At the time of the large immigration to Israel in 1951, diabetes was essentially nonexistent among the Yemenite Jews (25). Early studies performed between 1960 and 1971 by Altmann et al. (26) and Cohen (27,28) showed that the prevalence of diabetes in adults among newly arrived Yemenite Jews was lower (0.55%) than that

Table 3—*Incidence of childhood IDDM by age and ethnic groups in Israel, 1980–1993*

	Ashkenazi Jews			Non-Ashkenazi Jews			Israeli Jews			Arabs		
Age (years)	*n*	I	CI	*n*	I	CI	*n*	I	CI	*n*	I	CI
1980–1984												
0–4	6	1.7	0.3–3.1	8	1.5	0.4–2.5	17	1.9	1.0–2.8	7	1.2	0.3–2.1
5–9	20	4.8	2.7–6.9	21	2.8	1.6–4.0	24	3.8	2.3–5.3	12	2.2	0.9–3.4
10–14	45	11.1	7.9–14.4	42	5.4	3.8–7.1	22	5.8	3.3–8.2	14	3.0	1.4–4.5
15–17	16	7.1	3.6–10.6	31	7.4	4.8–10.0	12	8.6	3.7–19.4	10	4.1	1.6–6.7
1985–1989												
0–4	9	2.9	1.0–4.8	17	3.7	2.0–5.5	21	1.9	1.1–2.7	9	1.5	0.5–2.5
5–9	25	7.0	4.3–9.8	31	5.4	3.5–7.3	36	4.4	3.0–5.9	14	2.5	1.2–3.8
10–14	49	12.0	8.7–15.4	54	7.2	5.3–9.1	52	9.0	6.6–11.4	26	4.8	3.0–6.7
15–17	32	13.7	8.9–18.4	37	7.9	5.3–10.4	15	6.9	3.4–10.5	14	4.9	2.3–7.5
1990–1993												
0–4	10	3.1	1.2–5.0	16	5.4	2.8–8.1	14	1.4	0.7–2.2	8	1.5	0.4–2.5
5–9	32	8.9	5.8–12.0	26	6.7	4.1–9.3	51	6.0	4.4–7.7	16	3.4	1.7–5.1
10–14	58	16.0	11.8–20.1	45	9.5	6.7–12.3	54	8.7	6.4–11.0	13	2.9	1.3–4.4
15–17	31	11.9	7.7–16.1	35	9.4	6.3–12.5	35	13.3	5.9–17.8	14	5.4	2.6–8.2

Incidence rates are 10^5. I, incidence rate.

Table 4—*Relative risk estimates for the incidence of childhood IDDM in Israel according to age, ethnic group, and time-period*

Variable	Relative risk
Age (years)	
5–9	2.21 (1.80–2.69)
10–14	3.65 (3.00–4.48)
15–17	3.86 (3.16–4.71)
Reference group: 0–4 Years	
Origin (whole)	
Ashkenazi	1.48 (1.26–1.73)
Non-Ashkenazi	1.01 (0.86–1.19)
Arabs	0.54 (0.44–0.66)
Reference group: Israeli Jews	
Period (entire)	
1985–1989	1.35 (1.17–1.55)
1990–1993	1.55 (1.35–1.79)
Reference group: 1980–1984	

Data are relative risk (95% CI).

among established Yemenites and lower (1.1%) than that in Ashkenazi Jews. Cohen et al. (29) restudied 475 of his subjects between 1968 and 1977 and found that the prevalence of diabetes in these adults over 30 years old had risen to 12.6% in the Yemenites compared with 8.7% in the Ashkenazi Jews.

From our patient study it is evident that the Yemenite Jewish youth (0–17 years) have the highest incidence among the Jewish and non-Jewish ethnic communities in Israel ($18.5/10^5$), being similar to that reported from Kuwait for 1992–1993 in the age-group 1–14 years (19).

Despite the claim that the Jewish Yemenite population lived an isolated life with little integration with the non-Jewish population, the geographic proximity between Kuwait and Yemen—and the surprising finding of a very high and rapidly increasing incidence of childhood IDDM in these two seemingly genetically separate populations—raises the question whether over the centuries there was a possible contact between these two populations. Similar is the unexpected finding of the very sudden high incidence of childhood IDDM in Sardinia (16) compared with surrounding regions. The high incidence in Yemenite Jews and Kuwaiti Arabs is even more striking when compared with the very low incidence ($2.9–3.2/10^5$) among Israeli Arabs.

Preliminary studies by Israel et al. (30) have shown that the Yemenite Jews have a higher frequency of the genotype DR3. DQA1*0501/DQB1*0201 homozygotes are associated with IDDM mainly in the Yemenite Jews as is a high frequency of DR3/DR4 heterozygocity. In Kuwaiti children with IDDM, analyses of the frequency of HLA DQB1 alleles revealed a high frequency of non-Asp-57 alleles (31). The Yemenite Jews in Israel also seem to have an increased incidence of vitiligo (32), another autoimmune disease and coeliac disease (33). It is possible that the Yemenite Jews and Kuwaiti Arabs are genetically more susceptible to some β-cell toxic environmental factors, which have been introduced with the growing affluence in both countries. The basic difference in the incidence of IDDM between the Jews and Arabs is that the latter maintained a low incidence rate over years (7), and the difference between Ashkenazi, non-Ashkenazi, and Yemenite Jews can possibly be due to genetic factors influencing susceptibility to or protection from the autoimmune process of β-cell destruction.

However, the striking increase in childhood IDDM observed after 1985 in all ethnic subgroups of the Jewish population compared with the Arabs, as well as reports of an increase in incidence from other countries in various parts of the world (10–21), must be due to environmental agents linked to industrialization, with more pollution, the rapid economic rise leading to different lifestyles, changing methods in the food industry, and in nutritional habits, such as less breastfeeding, change in viral infections, etc. The Jewish population in Israel is mainly urban, whereas that of the Arabs mainly rural. The majority of Arabs and non-Ashkenazi Jews lead a more conservative lifestyle than the earlier emancipated Ashkenazi Jews and this may be part of the explanation. These differences in customs and environmental surroundings, in addition to some basic genetic differences in susceptibility to IDDM and other autoimmune (vitiligo) or immune diseases (asthma, coeliac disease) may explain why Israel is a country with a mixed (high, intermediate, and low) incidence of childhood IDDM.

As at the present time there is no cure for IDDM, a chronic disease with severe complications, the detection of the environmental pathogenic factors (viruses, nutritional factors, food additives, toxic substances, etc.) becomes a public health issue. Small countries like Israel with different ethnic populations, and differential changes in the incidence of IDDM, are ideal for the study and eventual detection of the β-cell pathogens.

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APPENDIX

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Kupat Holim Diabetes Clinics: Dr. E. Ben-Galim, Dr. A. Korkos (Jerusalem); Dr. D. Menuchin (Lin Clinic, Haifa); Dr. J. Arad (Rishon LeZion); Dr. Z. Lewinger (Petah Tikva); Dr. H. Crystal, Prof. B. Pade (Kiryat Shmona); Dr. Y. Yerushalmi (Tel Aviv).

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