Epidemiologic Survey of Juvenile-Onset Insulin Dependent Diabetes Mellitus (IDDM) in Hokkaido, Japan, 1973-1981


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Matsuura, N., Fukushima, N., Fujita, H., Abe, K., Yamada, Y., Kashiwao, N., Fujieda, K., Kato, T., Mikami, Y., Nohara, Y., Fukuda, K., Okuno, A., Taguchi, T. and Oyanagi, K. Epidemiologic Survey of Juvenile-Onset Insulin Dependent Diabetes Mellitus (IDDM) in Hokkaido, Japan, 1973-1981. Tohoku J. exp. Med., 1983, 141, Suppl. 181-189 — An epidemiological survey of juvenile-onset insulin dependent diabetes mellitus (0-15 years) was performed in Hokkaido, Japan, during 1973-1981. The mean annual incidence during the nine year period was 1.26 per 100,000 and showed a significant increasing trend. The prevalence of IDDM at the ages of 0-15 and 6-15 were 7.7 and 11.7 per 100,000 respectively. These figures were much lower than those previously reported in Caucasians. Peaks in incidence were seen from February to April, and a reduction in incidence from July to September. The females showed a bimodal distribution with the peak incidence at 10 to 12 years and with a smaller peak at about 7 years. The males showed a broad single peak at about 10 to 13 years. — juvenile-onset insulin dependent diabetes mellitus (IDDM); incidence; prevalence; seasonal variation

Although familial aggregation in juvenile onset insulin dependent diabetes mellitus (IDDM) has been recognized, the mode of inheritance remains to be elucidated. Great interest has recently been aroused by epidemiological studies on the noninheritable environmental factors which may be causal in IDDM. Adams1) reported in 1962 that the onset of IDDM showed a pronounced seasonal pattern, an observation which has been supported by reports from many countries in the northern hemisphere2-10) as well as in the southern hemisphere7,11). The close association of certain HLA types with IDDM has also been identified12).

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These studies supported the hypothesis that viral infection may play an etiologic role in the development of diabetes in the genetically predisposed individual.

Hokkaido is located in the northernmost part of Japan; its latitude corresponds to that of the northern part of the United States and its climatic changes are also similar to this region. Separated from the main island by the sea, Hokkaido covers an area of 83,511 km$^2$, and its population of 5.3 million is considerably lower than that of the rest of Japan (Fig. 1). The present report describes the incidence, prevalence, age at onset and seasonal variation of IDDM in the age groups 0–15 and 6–12 years during the nine year period from 1973–1981 in Hokkaido, Japan.

**Material and Methods**

The survey was limited to children who required insulin, and included all children who were less than sixteen years of age and who were residents of Hokkaido at the time of diagnosis. The one university medical school and two medical colleges in Hokkaido participated in the survey (Fig 1). The subjects were selected from among 1) patients who were admitted to the above three medical facilities; 2) children who had attended a summer camp for diabetic children 3) those who answered a questionnaire distributed to forty-one pediatric clinics in general hospitals and thirty-one internal medicine clinics in Hokkaido. Data were collected using a standardized form in which was recorded name, date of birth, symptoms and date of onset of symptoms, date of diagnosis and start of insulin treatment, laboratory data on admission and family history of insulin-dependent or noninsulin-dependent diabetes. The first survey was performed in 1973 when the above mentioned
A summer camp for diabetic children was started for the first time in Hokkaido. The survey has been repeated every January since 1977 up to January 1982.

**Statistical analysis.** The incidence of IDDM by sex, month and year was estimated based on the results of the 1975 National Census for persons aged 0 to 15. Since the number of males and females was about the same with little change over the year studied, a common population size of 699,000, the average of the two populations by sex, was used in the analysis. A three way analysis of variance (sex, month and year: binary type), and a linear regression analysis were utilized for the statistical tests.

**RESULTS**

A total of 191 cases of IDDM were registered in Hokkaido. Among these, 28 cases were diagnosed before 1973. The absolute number of cases of both sexes and the annual incidence per 100,000 for each three years from 1973 to 1981 are listed in Fig. 2, Table 1. Although there were some year to year variations, the annual incidence of IDDM in Hokkaido showed a steep increase. In absolute figures, the number of female cases exceeded that of the males, though this situation was reversed temporarily during the period 1978 to 1979.

The general seasonal trend can be seen in Fig. 3. As the number of cases in each year was so small, the total number of cases diagnosed per month was combined. Twenty-three cases which were detected by a urinary glucose screening program when they were asymptomatic were excluded from this figure. Peaks in incidence can be seen during the period from February to April and a reduction in incidence from July to September. A three way analysis of variance
TABLE 1. The annual incidence, by sex, of insulin-dependent diabetes mellitus (0-15 years) in Hokkaido, Japan and the comparison of findings in recent studies from other countries. (Mean yearly incidence per 100,000)

<table>
<thead>
<tr>
<th>Author</th>
<th>Age group</th>
<th>Male</th>
<th>Female</th>
<th>Combined sexes</th>
<th>Years of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsuura (Hokkaido, Japan)</td>
<td>0-15</td>
<td>0.63</td>
<td>1.20</td>
<td>0.91</td>
<td>1973-1975</td>
</tr>
<tr>
<td></td>
<td>0-15</td>
<td>1.49</td>
<td>1.20</td>
<td>1.34</td>
<td>1976-1978</td>
</tr>
<tr>
<td></td>
<td>0-15</td>
<td>1.58</td>
<td>1.73</td>
<td>1.66</td>
<td>1979-1981</td>
</tr>
<tr>
<td>Grosseley(18) (New Zealand)</td>
<td>0-15</td>
<td>8.6</td>
<td>9.2</td>
<td>9.0</td>
<td>1968-1972</td>
</tr>
<tr>
<td>Bloom(3) (England)</td>
<td>0-15</td>
<td></td>
<td></td>
<td>7.7</td>
<td>1973-1974</td>
</tr>
<tr>
<td>Lestrret(16) (France)</td>
<td>0-14</td>
<td></td>
<td></td>
<td>3.7</td>
<td>1975</td>
</tr>
<tr>
<td>Christau(6) (Denmark)</td>
<td>0-14</td>
<td>14.5</td>
<td>13.4</td>
<td>14.0</td>
<td>1970-1975</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonwhite</td>
<td>10.1</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>West(5) (Montreal, Canada)</td>
<td>0-17</td>
<td>8.6</td>
<td>9.0</td>
<td>8.8</td>
<td>1971-1977</td>
</tr>
<tr>
<td>Joner(4) (Norway)</td>
<td>0-14</td>
<td></td>
<td></td>
<td>17.6</td>
<td>1973-1977</td>
</tr>
<tr>
<td>Dahlquist(6) (Sweden)</td>
<td>0-14</td>
<td></td>
<td></td>
<td>22.6</td>
<td>1977-1980</td>
</tr>
</tbody>
</table>

Fig. 3. Seasonal variation of insulin-dependent diabetes mellitus (0-15 years) in Hokkaido, Japan.
revealed that a significant difference was observed only between years ($F_0 = 2.785 > F(8,\infty,0.01) = 2.51$). A subsequent linear regression analysis of the annual incidences showed a significant increasing trend ($t = 16.38$, degree of freedom = 7, $p < 0.01$). The age distribution at diagnosis in both sexes is shown in Fig. 4. The females showed a bimodal distribution with a peak incidence at about 10 to 12 years and with a smaller peak at about 7 years and the males demonstrated a broad single peak at about 10 to 13 years. Family histories with regard to diabetes are shown in Table 2. Among 191 children, 141 (73.8%) had no family history of the disease. Fifty (26.2%) children had a family history of diabetes involving a third degree relatives; and among these, fifteen had a history involving a first degree relative. However none of these were insulin dependent.

Numbers of children with IDDM at ages 0–15 and 6–15 were 108 and 98 respectively, all still living in Hokkaido at the end of 1981. The prevalence of IDDM in both age groups was 7.7 and 11.7 per 100,000 respectively. (Table 3)

**DISCUSSION**

The present survey disclosed that the incidence as well as prevalence of IDDM
was much lower in Japanese than in Caucasians as reported previously\(^\text{3,5,6,9,10,15,19}\). However, the incidence in Hokkaido showed a sharp increase during the nine year period (1973–1981). As the population size in our study was comparable to that of the previous studies, we concluded that the incidence of IDDM in the Japanese is much lower than in Caucasians.

Our method of ascertaining the number of cases was based on the assumption that all newly diagnosed IDDM are usually admitted into the hospitals which cooperated in this investigation. Moreover, the number can be verified by checking with urban and rural districts, which routinely keep records of the medical expenses incurred by IDDM patients.

**Annual incidence:** The mean annual incidence of IDDM in Hokkaido during the nine year period was 1.26 per 100,000. This figure is about 1/6 to 1/20 of that reported previously for Caucasians\(^\text{3,5,6,9,10,15,19}\). The reasons for the low incidence in the Japanese and the significant increase of incidence in Hokkaido remain to be elucidated. Environmental factors such as socioeconomic influences, nutrition, viral infection together with genetic factors were considered to be responsible. Also considered was fact that the average annual Japanese income has increased steadily during the past ten to twenty years so that it is now almost equal to that of Americans and Europeans. Moreover, there have been rapid changes in Japanese lifestyle and eating habits toward those of Western countries. Changes in the Japanese diet include an increased consumption of sugar-loaded beverages, carbohydrates, saturated fats and high salt-instant foods. Some different genetic factors may also play a role in instigating the disease. The association between HLA-B8-DR3-DW3 and/or B15-DR4-DW4 haplotypes and

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**TABLE 3. The prevalence of insulin-dependent diabetes mellitus (0-15 years) in Hokkaido, Japan and the comparison of findings in recent studies from other countries**

<table>
<thead>
<tr>
<th>Author</th>
<th>Years of study</th>
<th>Age group</th>
<th>No. of children ((\times 10^4))</th>
<th>Prevalence per 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsuura (Hokkaido, Japan)</td>
<td>1979</td>
<td>0–15</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>1980</td>
<td>0–15</td>
<td>140</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>1981</td>
<td>0–15</td>
<td>84</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–15</td>
<td></td>
<td>1.17</td>
</tr>
<tr>
<td>Lestrade (France)</td>
<td>1975</td>
<td>0–14</td>
<td>1,258</td>
<td>2.4</td>
</tr>
<tr>
<td>Gorwitz (Michigan, U.S.A.)</td>
<td>1976</td>
<td>5–17</td>
<td>172</td>
<td>16.1</td>
</tr>
<tr>
<td>Kyllö (Minnesota, U.S.A.)</td>
<td>1978</td>
<td>5–17</td>
<td>87</td>
<td>18.9</td>
</tr>
<tr>
<td>Dahlquist (Sweden)</td>
<td>1980</td>
<td>0–14</td>
<td>26</td>
<td>14.8</td>
</tr>
</tbody>
</table>
IDDM has been reported in Caucasians\(^{12}\). Moreover, it has been suggested that the effects of these two antigens are additive\(^{12}\). On the other hand, we have found association of the HLA-BW54-CW1-DR4-MT3 haplotype in Japanese\(^{20}\). In particular, an almost perfect association was observed between DR antigen, MT3 in the Japanese. Rotter\(^{12}\) reported that there are two distinct forms of IDDM; one is associated with HLA-B8-DR3 and the other with HLA-B15-DR4. It would reasonable to speculate that only one of these types occurs in the Japanese; this would account for the much lower incidence than seen in Caucasians. However, Waxman\(^{21}\) reported that the incidence of IDDM in Americans of Japanese parentage living in Hawaii did not differ from that of Caucasians. These facts together with the increasing changes in the Japanese lifestyle suggest that environmental factors may be more important than genetic factors in the development of IDDM.

**Age and Sex:** Previous studies have suggested a bimodal distribution of the age of onset in IDDM\(^{3,6,9,10}\). In the present work, such a bimodality was seen only in females in contrast to reports from Sweden\(^{10}\) and Norway\(^{9}\) where a bimodality was noted only in males. The early peak has been associated with the start of school when major environmental changes occur and the high incidence in both sexes in the prepubertal and pubertal years have been associated with the growth spurt. In the present study, the increases in incidence occurred earlier in females than in males as previously reported\(^{3,5,6,7,9,10}\).

**Seasonality:** Our study showed increased incidence during the winter months and decreased incidence during summer months. However, the three-way analysis of variance did not reveal a significant difference between the months. The general trend towards more new cases in the winter months has been observed in the northern hemisphere\(^{2-10}\) as well as in the southern hemisphere\(^{7,11}\). The seasonal variations are generally believed to reflect the influence of environmental factors such as viral infection, lack of exercise etc. The seasonal variations were observed only in certain age groups and were sex-specific\(^{2-7}\).

**Family History:** History of diabetes involving a first degree relative was seen in 15 cases out of the 191 examined (7.9%); however, none of the parents were insulin dependent. Between 10 to 14.5% of Caucasian patients have been reported to have an insulin dependent first relative\(^{3,5,10}\).

In conclusion, this comprehensive nine-year study has shown for the first time the prevalence, incidence, age at onset and seasonal variation of IDDM in children aged 0-15 years in Japan. We found a marked difference in incidence and prevalence as compared with Caucasians. Further epidemiological studies are necessary to clarify what genetic differences, and environmental factors play a role in the etiology of IDDM.

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References


