The Clinical Features of Diabetes Mellitus in Japan as Observed in a Hospital Outpatient Clinic

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SUMMARY

A University diabetes clinic in Japan was characterized in terms of age, age at "onset," sex ratio, microangiopathies, neuropathy, atherosclerotic complications, weight, heredity and diet. The findings in this clinic, along with those from other diabetes clinics in Japan, were compared with studies on Western diabetics. The similarities between the two diabetic populations in clinics far outnumbered the dissimilarities. However, diabetes mellitus in Japanese diabetes clinics is distinguished by the infrequent occurrence of juvenile diabetes and ketosis, relative lack of atherosclerotic complications and reversal of the sex ratio.

INTRODUCTION

The prevalence of diabetes in Japan is comparable to that in Western countries. Diabetes detection programs in Japan and the United States have revealed prevalence rates greater than 4 per cent in persons over age forty. Detection of diabetes depends, however, on only one parameter of this multifaceted disease—the carbohydrate disturbance. All persons with carbohydrate intolerance characteristic of diabetes mellitus may not necessarily have the same disease. The clinical variations with age at onset, body build, race and geographic location suggest several different disease entities with a common means of detection.

The purpose of this report is to describe the clinical features of diabetes mellitus seen in hospital outpatient clinics in Japan and to compare the findings with those of similar studies reported from Western countries. Although the comparisons were made using selected diabetic populations in clinics, we hoped to determine whether diabetes in Japan resembles that seen in the West.

SUBJECTS AND METHODS

The Hiroshima University hospital receives the majority of its patients from Hiroshima City. Twenty per cent of the patients are doctor referrals, and as in University hospitals in the West, the disease spectrum seen is probably overbalanced with chronic and difficult diagnostic problems. Approximately 90 per cent of the patients have health insurance and are in the economic middle class. The remainder are the extremely wealthy or the extremely poor, predominantly the former. All diabetics detected at the hospital are advised to return regularly to the diabetes clinic regardless of the severity of their disease. It is possible, however, that the symptomatic diabetics present themselves at the clinic more regularly than the asymptomatic ones.

During a five-month period from August through December 1962, approximately 100 diabetic patients were seen in the Hiroshima University diabetes clinic. Ninety-one of these patients cooperated by permitting ophthalmologic consultation and interview by the dietitian. These subjects form the basis of this report.

Clinical evaluation included a history of the age at "onset" of diabetes (herein defined as time of diagnosis or onset of typical symptoms), and of diabetes in the family. Weights were determined at the time of examination. Percentage deviation from standard weight was calculated from tables constructed for Japanese subjects. The standard weights are 5 per cent below those usually recorded for Western persons of the same height. In addition, weight percentiles by age, height and sex were derived for each patient from data on the Atomic Bomb Casualty Commission (ABCC) clinic populations in Nagasaki and Hiroshima.

Coronary artery disease was diagnosed if the patient had electrocardiographic evidence of myocardial infarction in the past or a history of angina agreed upon by two observers. The diagnosis of peripheral vascular disease was based on a history of intermittent claudica-
tion or the presence of gangrene. The diagnosis of cerebrovascular accident was made from history and physical examination. In examination for hypertension, two blood pressure readings five minutes apart were taken from the right arm with the subject supine. Hypertension was diagnosed if the lower reading included a systolic pressure above 150 mm. Hg. or a diastolic pressure above 90 mm. Hg. Knee and ankle reflexes were tested with and without reinforcement procedures for evidence of neuropathy. All subjects were seen in the Ophthalmology Clinic by one of the authors (ST). After dilation of the pupil with 5 per cent phenylephrine, the fundi were examined by direct and indirect ophthalmoscopy. In several questionable cases, slit lamp examination of the retina with Hruby lens was performed. Abnormal fundi were graded according to Scott’s criteria.7

The sulfosalicylic acid test was employed for detection of proteinuria. Urine ketones were not routinely tested.

A dietitian recorded for each patient a history of dietary habits covering the past twenty years. These histories represented only a gross approximation of the average diet during this period. If changes in diet had occurred, they were weighted according to the length of time the patient had been on the different diets. Changes within the past two years were not included in this survey as only an estimate of the dietary composition over a twenty-year period was desired.

Clinical and dietary data from the four diabetic patients below the age thirty are omitted in all but the first table characterizing the age distribution of the diabetes clinic. The remaining eighty-seven patients may be considered by definition adult-onset diabetics.

RESULTS AND DISCUSSION

1. Age, age at “onset” of diabetes, and sex. Table 1 shows the age distribution and age at “onset” of disease for ninety-one patients in the Hiroshima University diabetes clinic. As in Western diabetics,8 the age at “onset” is most commonly the fifth and sixth decades. Only one juvenile diabetic with “onset” of disease before age fifteen was observed in our clinic whereas juvenile cases account for 5 to 10 per cent of diabetics in Western clinics.9 Review of the past 20,000 records on pediatric inpatients and outpatients in the Hiroshima University Hospital for the past ten years revealed only three cases of diabetes mellitus. (Personal communication from A. Nakamor.)

In contrast to the preponderance of females in most Western diabetes clinics,10 males outnumbered females by 15 per cent in our clinic. Sex prevalence rates in diabetes detection programs in the two populations confirm this variation in sex ratio. A detection program in Oxford, Massachusetts,4 revealed a male : female ratio of 0.8:1 in persons over age forty-four. In a detection program in Hiroshima, Japan,9 the sex ratio of diabetics over age forty was 2.4:1 in favor of males. Although there were only slightly more males than females in our clinic (M:F, 1.2:1), other clinics in Japan have ratios more consistent with that of the Hiroshima detection program (Tohoku University, 2:1;12 Tokyo University, 3:1).12

2. Heredity. Family histories of at least one relative having diabetes were elicited in 15 per cent of the patients. Eight other Japanese clinics have reported positive family histories in 5 to 21 per cent of their diabetic patients.13 In a diabetes detection program in Hiroshima, 23 per cent of the diabetics and 1.7 per cent of the nondiabetics had positive family histories of diabetes.3 In a nationwide survey, Kobayashi and co-workers1 have reported that 7.6 per cent of diabetics and 2.5 per cent of nondiabetics had hereditary histories of diabetes.9

In a nationwide survey, Kobayashi and co-workers1 have reported that 7.6 per cent of diabetics and 2.5 per cent of nondiabetics had hereditary histories of diabetes. The frequency with which a positive family history is obtained varies widely as it does in Western studies (19-41 per cent).8 It would appear, however, that a positive family history is obtained less frequently in Japanese than in Western diabetics. One reason for this difference may be related to the somewhat greater occurrence of undetected diabetes in Japan. Over 50 per cent of the diabetics in the Hiroshima detection program had previously undetected disease3 compared to 42 per cent in the Oxford, Massachusetts, survey.4 Only by actual testing of family members can a true hereditary pattern be established.

3. Weight. The association between overweight and diabetes is well known. The majority of Western dia-
The weight distribution of Japanese diabetic subjects may be seen in table 2. Twenty-nine per cent of our patients were more than 10 per cent overweight. Similar results were recorded by Satoshi and co-workers at Keio University. In a diabetes detection survey in Hiroshima in which a large percentage of patients were diagnosed for the first time, 45 per cent of the females and 40 per cent of the males were more than 10 per cent overweight. There are two possible explanations for the larger percentage of overweight diabetics in a detection program than in a diabetes clinic. The clinic diabetics probably had been symptomatic and had lost weight as a result of the disease whereas in a detection program, new diabetic cases would be asymptomatic with little weight loss. Also, weight reduction had been prescribed for many of the diabetes clinic patients. Such variations in weight data between a detection program and a clinic and the variations in the same patient at different times make reliance on comparison between Japanese and Western findings hazardous.

### TABLE 2

<table>
<thead>
<tr>
<th>Deviation from Standard Weight</th>
<th>Hiroshima University Male (Per cent)</th>
<th>Hiroshima University Female (Per cent)</th>
<th>Total (Per cent)</th>
<th>Hiroshima Atomic Bomb Casualty Commission Male (Per cent)</th>
<th>Hiroshima Atomic Bomb Casualty Commission Female (Per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight ±10 per cent</td>
<td>37</td>
<td>61</td>
<td>48</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Underweight more than −10 per cent</td>
<td>33</td>
<td>12</td>
<td>23</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Overweight +10 per cent to +20 per cent</td>
<td>17</td>
<td>5</td>
<td>12</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Obese more than +20 per cent</td>
<td>13</td>
<td>22</td>
<td>17</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

The percentage of individuals more than 10 per cent overweight in the Hiroshima University diabetes clinic is similar to those recorded for a nondiabetic Western population. Pyke and Pease reported that 27 per cent of normal women and 21 per cent of normal men exceed their standard weight by more than 10 per cent after the age of forty. Suitable weight statistics in Japanese nondiabetics are not available for comparison with those in our diabetes clinic. However, 39 per cent of our diabetic patients were in the upper 25 weight percentiles for their age, sex and height. (This information was derived from data on the ABCC clinic populations in Nagasaki and Hiroshima. Although currently it is suspected that overweight is not as prominent a feature of diabetes in Japan as in Western countries, it does occur more frequently in diabetics than in nondiabetics.

4. **Ketosis.** No patient gave a history of diabetic acidosis. Ketosis is believed to be rare in Japan. A review of the Japanese literature from 1915 to 1957 by Goto and Muraki uncovered only 103 reported cases of diabetic acidosis. Unfortunately, ketonuria was not investigated routinely in our clinic. In a diabetes clinic at Osaka Medical College, Yoshida reported ketonuria in 5.4 per cent of patients under forty and in 1.7 per cent of patients over forty during their initial clinic visit. Reports from eight other Japanese clinics indicate that 2 to 11 per cent of all diabetic clinic patients had ketonuria before treatment. In comparison, Freeman observed ketonuria in 43 per cent of 300 British diabetic subjects at initial examination.

5. **Vascular Disease and Neuropathy.** In tables 3 and 4 are given the prevalences of vascular disease and neuropathy.

Microangiopathies are regarded as lesions quite specific for diabetes seen in Western countries. The involvement of small vessels is widespread and is most evident clinically in retinopathy and nephropathy. The numerous proposed causes of microangiopathies and the lack of acceptance of any single one suggest that they are an integral part of the disease rather than a complication. This study directs particular attention to retinopathy, the most common manifestation of microangiopathy.

The distribution of diabetic retinopathy (Scott's criteria) in our clinic is shown in table 3. Similar to studies in the West, retinopathy occurred in direct proportion to the duration of diabetes. Reports from three other Japanese universities have shown a slightly lower prevalence of retinopathy (Tohoku University, 27 per cent; Keio University, 28 per cent; Nara Medical College, 37 per cent). However, retinopathy occurred more frequently in females in all series, and the larger number of women in the Hiroshima clinic may well explain the higher over-all prevalence of retinopathy in that clinic.

Prevalence of retinopathy by sex and duration of disease in Western countries could not be found for comparison. However, Western figures show that retinopathy occurs in over 75 per cent of persons having diabetes fifteen years or more. Our figures indicating retinopathy in 71 per cent of all patients with disease
TABLE 3
Retinopathy in the Hiroshima University Diabetes Clinic

<table>
<thead>
<tr>
<th>Complication</th>
<th>All patients (per cent)</th>
<th>Male (per cent)</th>
<th>Female (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>46 (39)</td>
<td>11 (23)</td>
<td>35 (16)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>46 (26)</td>
<td>23 (15)</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Neuropathy (absent reflexes)</td>
<td>32 (22)</td>
<td>14 (19)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (23)</td>
<td>1 (20)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>2 (7)</td>
<td>1 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (4)</td>
<td>3 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses represent number of patients.

TABLE 4
Prevalence of vascular disease and neuropathy in the Hiroshima University Diabetes Clinic (eighty-seven patients)

<table>
<thead>
<tr>
<th>Duration of disease</th>
<th>All patients</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20 yrs.</td>
<td>60 (3)</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>10-19 yrs.</td>
<td>50 (4)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1-9 yrs.</td>
<td>36 (44)</td>
<td>13 (21)</td>
<td>23 (16)</td>
</tr>
<tr>
<td>&lt; 1 yr.</td>
<td>24 (39)</td>
<td>11 (21)</td>
<td>13 (16)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses represent number of subjects with retinopathy.

more than fifteen years and in 100 per cent of females with disease more than ten years are compatible with Western findings. These figures exclude the one patient in whom the diagnosis of retinopathy was based only on phlebosclerosis. In Scott's British series, over 75 per cent of the diabetes with retinopathy had mild changes with venous distention, capillary microaneurysms or small punctate hemorrhages with or without discrete flecks of exudate (Scott's Stage I or II) while 9.7 per cent had retinitis proliferans. In the Hiroshima University clinic, 57 per cent of the retinopathy patients had Stage I or II mild changes and 9 per cent had retinitis proliferans. These results indicate that retinopathy is as frequent and as severe in a Japanese diabetes clinic as in Western diabetes clinics.

There is sparse and conflicting information available on the prevalence of retinopathy by sex in Western diabetes clinics. In our clinic, not only was retinopathy more frequent in females but it also appeared to be more severe. By Scott's criteria, 71 per cent of the males with retinopathy had mild changes (Stage I or II) while only 50 per cent of the females with retinopathy had these minimal changes. All three patients with retinitis proliferans or retinal detachment (Stages V and VI) were females.

Table 4 records also the frequency of proteinuria and neuropathy (absent patellar reflexes) in the Hiroshima University diabetes clinic. Proteinuria and neuropathy as well as retinopathy were more prevalent in females in our clinic. This triad of complications, retinopathy, nephropathy, and neuropathy, frequently called diabetic triopathy, occurred in 8 per cent of our patients, six of whom were females. Again, there are few comparable studies in the West; however, of 2,288 diabetics admitted to the New England Deaconess Hospital during 1953, 17.9 per cent had retinopathy, 9.5 per cent had nephropathy, 13.1 per cent had neuropathy, and 3.1 per cent had triopathy. The low occurrence of these complications in the Deaconess Hospital may be attributed to more stringent criteria for diagnosis (18 per cent of our patients with retinopathy would not have been included). Also, figures on unselected diabetic inpatients may not represent the frequency of complications seen in a diabetes clinic. In a Western diabetes clinic MacNeal and Rogers observed proteinuria in only 8 per cent and neuropathy (absent patellar reflexes) in only 2 per cent of their 103 diabetic patients. Broch and Klovstad of Norway reported areflexia in 18.7 per cent of their diabetic patients. Our findings indicate a somewhat greater frequency of these complications in Japanese diabetes clinics. The occurrence of proteinuria (30 per cent) in the Tohoku University diabetes clinic and the occur-
rence of areflexia (29 per cent) in the Osaka Medical College diabetes clinic support our data.

It would appear that retinopathy, nephropathy, and neuropathy are as common in diabetes clinics in Japan as in the West.

Since atherosclerosis is reported to be infrequent in Japan, hypertension is believed to be a major contributing factor to cerebral vascular accidents in Japan. According to the diagnostic criteria outlined above hypertension was found in 23 per cent of the patients. This prevalence does not differ significantly from the 20 per cent rate for hypertension among nondiabetic patients of the same age and sex in the Hiroshima ABCC clinic, but it is lower than that in other Japanese diabetes clinics (Tohoku University, 38 per cent; Tokyo University, 37 per cent; Osaka Medical College, 34 per cent).

History and physical signs of a previous cerebral vascular accident were present in 7 per cent of our diabetic subjects. Only 1 per cent of an unselected local population of the same age and sex would be expected to have had a nonfatal stroke according to prevalence rates by age and sex in the ABCC clinic subjects. Even if all patients had been hypertensive, a nonfatal stroke would be expected in only 5.3 per cent.

Japan's reported death rate due to coronary artery disease is one of the lowest in the world. For this reason we anticipated a low occurrence of coronary artery disease in Japanese diabetics. The prevalence of coronary artery disease (angina pectoris or myocardial infarction) in our clinic was 5 per cent. Although the absolute number of cases is small in our series, the percentage is consistent with that observed in other Japanese diabetes clinics (Tohoku University, 5.8 per cent; Tokyo University, 7 per cent; Osaka Medical College, 3 per cent). From prevalence rates in the 13,000 person ABCC clinic in Hiroshima only 1 per cent of an unselected population of the same age and sex as our clinic diabetics would be expected to have coronary artery disease.

None of our patients had gangrene or intermittent claudication whereas gangrene was present in 2 per cent of the Tokyo University diabetes clinic. In a Western diabetes clinic of similar age distribution, the prevalence of peripheral vascular disease was 32 per cent as detected by diminished foot pulses, gangrene or a history of intermittent claudication. In another study in the United States gangrene was present in 6.4 per cent of cases.

6. Diet. The apparent rarity of atherosclerotic complications in Japan has been attributed to the low fat diet ingested by Japanese people. Although earlier studies had indicated a retardation of atherosclerotic complications in Western diabetics on a low fat diet (50 gm.), recent investigations have cast some doubt on this relationship. Albrink, Lavietes and Mar have suggested that high calories, not high fat, make a diet atherogenic. The Japanese diet would be nonatherogenic on either score. In addition, there are now observations on the beneficial effect of low fat diets on diabetic retinopathy. These benefits, however, seem limited mainly to clearing of exudates. Because of the improvement noted in diabetic retinopathy in Western patients taking 20 gm. fat diets and in patients on the low fat Kempner rice diet, it was anticipated that there might be dietary differences between diabetics with and without retinopathy. To investigate this possibility a dietary recorded dietary histories covering the previous twenty-year period for all patients.

Shown in table 5 are the percentages of diabetics with and without retinopathy who daily took over 30 gm. of fat. With few exceptions, patients taking over 30 gm. of fat daily derived more than 10 per cent of their calories from fat whereas those taking less than 30 gm. daily obtained less than 10 per cent of their calories from fat. The percentage of persons on high fat diets was twice as great in the diabetics with retinopathy as in those without retinopathy. But when the correlation between diet and duration of disease was examined, it was observed that the percentage of patients with high fat intake increased with the duration of disease, irrespective of the retinal state. Although there was a relationship between retinopathy and high fat diets, this appeared to be due to the longer duration of disease in patients with retinopathy. The conclusion that diabetics with long duration of disease

| TABLE 5 |
| Relationship of high fat diet (over 30 gm. per day) to occurrence of retinopathy and duration of disease |

<table>
<thead>
<tr>
<th>Retinopathy present</th>
<th>Retinopathy absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Per cent on high fat diet</td>
</tr>
<tr>
<td>All patients</td>
<td>34</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td></td>
</tr>
<tr>
<td>≤ 5 yrs.</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 5 yrs.</td>
<td>26</td>
</tr>
<tr>
<td>&gt; 10 yrs.</td>
<td>13</td>
</tr>
</tbody>
</table>

*Numbers in parentheses represent number of patients on high fat diet.
alter diets to take more fat seems the best explanation for these findings. This had not been anticipated as less than half of the patients had been given specific diet instructions and had been told only to decrease their caloric and carbohydrate intake. After completion of the study, reinterviews with some of the patients revealed that diets were frequently changed on the advice of neighbors or from information in lay diabetes journals. The large percentage of high fat diets in subjects with retinopathy and disease duration less than five years cannot be explained. However, the number of diabetics in this group is quite small. From this study, it is impossible to say that dietary fat plays no role in the development of retinopathy. But the fact that retinopathy appears to be as common in Japan where average fat intake is approximately 20 gm. as in the United States where average fat intake is 110 gm. makes it unlikely that dietary fat plays a significant role in the development of retinopathy.

SUMMARIO IN INTERLINGUA

Le Characteristicas Clinic de Diabete Mellite in Japon, Secundo Observationes in un Clinica Hospitalari pro Patientes Visitante

Le casuistica de un clinica universitari pro diabeticos in Japon es characterisate secundo etates, etates al tempore del declaration del morbo, proportion del sexos, microangiopathias, neuropathia, complicaciones atherosclerotic, peso, hereditate, e dieta. Le constatationes, supplementate per alteres obtenite ab altere clinicas pro diabeticos in Japon, eseva comparate con studios in diabeticos occidental. Le similitudines eseva plus numerose que le dissimilitudes. Tamen, diabete mellite in japones clinicas pro diabeticos es characterisate per le infrequentem occurrentia de diabete juvenil e de cetonias, per le relative raritate de complicaciones atherosclerotic, e per un reversion del proportiones sexual.

ACKNOWLEDGMENT

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REFERENCES

We soon found that to prepare for each forum properly it was necessary to have two meetings of from one to two hours each of the members of each panel prior to the forum. It was also evident that the moderator’s ability to handle the panel had much to do with its success and the success of the future forums. Frequently, the moderator had to terminate the discussion at the end of two hours because the number of questions was so great there was insufficient time to answer all of them. At some forums, the question period would have been prolonged another hour if there had been time. Many of the questions have been kept on file. Some questions could not be answered in public and have been answered in private after the forum. Most of the questions were intelligent and directly related to the panelists’ discussion. Occasionally, we would have to refer the questions back to the family physician. Informal, direct conversation with some members of the audience at the end of the forum has been very interesting and helpful.

Sixty-five physicians have participated in these forums. The following specialties have been represented: internal medicine, neurosurgery, general practice, ophthalmology, oto-rhinolaryngology, pediatrics, obstetrics and gynecology, psychiatry, surgery, public health, orthopedic surgery, roentgenology, dermatology, proctology and thoracic surgery.

Total attendance has exceeded 6,000. However, these forums have reached a far larger number of people than the seating capacities of the hospital auditoriums would permit. The local newspaper, the Niagara Falls Gazette, has aided greatly the preforum publicity with excellent articles regarding each forum. The cooperation of the local newspaper was obtained by one of the members of the Public Forum Committee who visited the editor and convinced him that the forums would be of great benefit to the public, especially so if the newspaper published what was said by the panelists. For many years the Niagara Falls Gazette has been very cooperative in publishing medical events and news and has reported in considerable detail the discussions at the forums.

CONCLUSIONS

After holding public medical forums for six years and observing the enthusiastic acceptance of these forums, it is evident that more hospitals and their medical staffs should organize similar projects. The general public feels that physicians, as a whole, do not do much for them except individually. It is difficult for the hospitals to participate in community activities, and these forums give hospitals and physicians a direct means of offering public service. The wide variety of questions asked by the audience has revealed that some of the public has a considerable knowledge of medicine.

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