The insulin and glucose response to an oral glucose load in non-insulin-dependent diabetes in the young

I. JIALAL, S. M. JOUBERT, A. C. ASMAL, N. JENKINS

Summary
Non-insulin-dependent diabetes with age of onset under 35 years was studied in 85 Indian patients. Eighty-one per cent of the group were females, the mean age of onset of diabetes was 27 years while the mean duration was 6.3 years. The mean percentage desirable mass of the patients was 122%, obesity being present in 55% of the group. Eighty-two per cent of patients gave a positive family history; closer analysis revealed that 75% of the propositi had a diabetic parent and 41% a diabetic sibling; while three-generation transmission was present in 7%.

Eighty-one patients consented to a 100 g oral glucose load. The insulin and glucose response during a 3-hour period revealed fasting hyperinsulinism with a delayed and attenuated insulin response, a much lower insulin area and higher glucose area, hyperinsulinism with a delayed and attenuated insulin response, a much lower insulin area and lower insulin levels at all times, except in the fasting state, during which the insulin levels were not significantly different.

Fajans and Conn1 were the first to draw attention to the occurrence of mild diabetes in young people which responded by improvement of glucose tolerance with tolbutamide therapy. Similar studies confirming this entity were subsequently reported from Scandinavia, England and the USA.2-4

About the time Fajans and Conn reported their study, Campbell5 drew attention to the existence of insulin-dependent diabetes in young Natal Indians; more recently, Jackson6 stated in a review that whereas insulin-dependent diabetes is extremely rare in young South African Indians, a maturity-onset type of diabetes in the young (MODY) is fairly common. In a preliminary report certain aspects of non-insulin-dependent diabetes with onset below 35 years in 43 Indian and 9 Black patients were considered.7

In the present study, which is part of an ongoing study of this type of diabetes, we wish to report in greater detail on the clinical features in 85 Indian patients as well as on the glucose and insulin response to a 100 g oral glucose load.

Patients and methods

Non-insulin-dependent diabetes in the young (NIDDDY) was categorized according to the following criteria: age of onset

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under 35 years; duration of diabetes greater than 1 year; ketonuric but symptomatic presentation; prevention of ketonuria and satisfactory control of symptoms without insulin therapy. In addition all patients studied satisfied the criteria of the World Health Organization for the diagnosis of diabetes: fasting plasma glucose level ≥ 8 mmol/l and/or ≥ 12 mmol/l/12 hours after 100 g oral glucose. Over a 3-year period 85 Indian patients fulfilled the stated criteria and were entered into the study. The reference group comprised 50 randomly drawn apparently healthy Indians (25 males and 25 females) in the same age range as the patients. It must be stressed that the reference subjects were not matched for age, weight and sex and the only purpose the group served was to establish the insulin and glucose response in non-diabetic and apparently healthy Indians in the same age range as the patients. Informed consent was obtained from all participants in this study.

Since the majority of patients were on oral hypoglycaemic agents and a low-carbohydrate diet, they were advised to discontinue therapy and to eat higher-carbohydrate mixed diets for a period of 3 days prior to testing. Eighty-one diabetic patients and 50 reference subjects were given 100 g oral glucose dissolved in 250 ml water after an overnight fast. Blood samples were withdrawn before, and at 15-minute intervals for the 1st hour and thereafter at 30-minute intervals for the next 2 hours via an indwelling cannula in a deep antecubital vein.

Blood samples were collected in potassium oxalate-fluoride tubes and glucose was measured by the Technicon AutoAnalyzer using the modified ferricyanide method of Hoffman. Immunoreactive insulin in serum was estimated by radioimmunoassay, in which the antibody is coupled to a solid phase (Pharmacia, Uppsala, Sweden). The percentage desirable mass was calculated from Tables 1 and 2.

Results

Clinical features

The essential clinical findings are summarized in Table I, from which it can be seen that 81% of the group were females. This predominance of women should be qualified, for it is well known that among Indians in Natal the women tend to support hospital clinics whereas men prefer private or company medical services.

Duration of diabetes exceeded 1 year in all patients, with a mean of just over 6 years. The mean percentage of desirable mass (≥ 120% of desirable body mass) being present was 55%. The mean age of onset was 27 years and a high percentage had a positive family history (82%). In Table II the family histories are analysed in greater detail; 75% of the patients had a diabetic parent and 41% of the patients had a diabetic sibling. Six patients (7%) gave a history of diabetes extending through three consecutive generations.

Glucose and insulin responses during glucose tolerance testing

In Figs 1 and 2 the plasma glucose and serum immunoreactive insulin levels for the reference group (controls) and patients are presented in graphic form. The responses of the reference group for both glucose and insulin are within accepted ranges for normal non-diabetic subjects, whereas in the patient group both the glucose and insulin responses were consistent with severe non-insulin-dependent diabetes. The fasting insulin levels were significantly greater than in the reference group (25,31 ± 1,38 v. 14,63 ± 0,73 μU/ml; P < 0,001). Although the diabetic group had higher insulin levels at 180 minutes (45,38 ± 3,38 μU/ml) compared with the reference subjects (39,9 ± 2,43 μU/ml), this did not attain significance at the 5% level.

Relevant correlations between variables were undertaken.

<table>
<thead>
<tr>
<th>TABLE I. CLINICAL CHARACTERISTICS OF 85 PATIENTS WITH NIDDY</th>
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<tbody>
<tr>
<td>Male-to-female ratio</td>
</tr>
<tr>
<td>Family history of diabetes</td>
</tr>
<tr>
<td>Age of onset (mean and range)</td>
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<tr>
<td>Duration of diabetes (mean and range)</td>
</tr>
<tr>
<td>Percentage desirable mass (mean and range)</td>
</tr>
<tr>
<td>Percentage with obesity (mass ≥ 120% of desirable mass)</td>
</tr>
</tbody>
</table>

Fig. 1. Insulin response to a 100 g oral glucose load in controls and patients with Niddy (mean ± SEM).

Fig. 3 shows that the area under the insulin curve is much lower in the diabetics than in the controls (108,16 ± 6,12 and 200,69 ± 10,50 μU/ml respectively; P < 0,001) while the area under the glucose curve is much greater in the diabetics (47,49 ± 1,34 v. 13,41 ± 0,33 mmol/l; P < 0,001).

Insulin-glucose ratios were calculated as a measure of the hormonal output per unit of glycaemic stimulus. At all time intervals during the glucose loading, the diabetic group had a much lower ratio (Table III). Comparisons of the ratios of the
Fig. 2. Plasma glucose response to 100 g oral glucose in controls and patients with NIDDY (mean ± SEM).

**TABLE III. INSULIN-GLUCOSE RATIOS AND MODIFIED INSULINOGENIC INDEX IN NON-DIABETIC CONTROLS AND NIDDY**

<table>
<thead>
<tr>
<th>Insulin-glucose ratios (mean ± SEM)</th>
<th>Controls (50)</th>
<th>NIDDY (81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>0.19 ± 0.01</td>
<td>0.13 ± 0.01*</td>
</tr>
<tr>
<td>60 min</td>
<td>1.05 ± 0.08</td>
<td>0.14 ± 0.01*</td>
</tr>
<tr>
<td>120 min</td>
<td>0.82 ± 0.05</td>
<td>0.15 ± 0.01*</td>
</tr>
<tr>
<td>180 min</td>
<td>0.59 ± 0.04</td>
<td>0.16 ± 0.02*</td>
</tr>
<tr>
<td>MSI</td>
<td>0.87 ± 0.05</td>
<td>0.14 ± 0.01*</td>
</tr>
</tbody>
</table>

*P < 0.001.
MSI = modified Seltzer insulinogenic index.

Discussion

It should be emphasized that the selection of patients was dominated by the need to identify unequivocally the existence of NIDDY in Indians and this purpose was achieved. But it should be borne in mind that the group is heterogeneous in respect of duration of disorder, treatment offered and success with which it was applied, all of which would have a bearing on metabolic studies. The selection also favoured those patients with severe diabetes so that the sample is not representative of the Indian community.

In common with most previous reports women were the dominant sex, but this finding may relate to local custom rather than real prevalence of the disorder in the two sexes.

By far the most striking clinical feature of NIDDY in Indian patients is the familial aggregation of the disorder. In this respect the group closely resembles the patients previously described. In the present study 75% of patients had a diabetic parent and 41% a diabetic sibling, as opposed to the 85% with a diabetic parent and 53% with a diabetic sibling reported in previous studies. The present findings differ from previous studies in that only 6 patients (7%) were found with a three-generation family history as opposed to the 46% reported by Tattersall. However, the socio-economic circumstances of Indians 40 - 60 years ago and the availability of medical services generally in South Africa were such that it would be surprising if present-generation Indians knew from what medical disorders their grandparents suffered. This aspect of three-generation transmission can be settled only by prospective study.
Nevertheless, it is believed that the familial aggregation in the present study is unique enough to differentiate the condition from non-insulin-dependent diabetes in the older age group, since the presence of a positive family history in 82% is far in excess of the 48% reported by Campbell and McKeechnie in older non-insulin-dependent diabetics. In view of the similarities in the high percentages of parent and sibling diabetics which could be accurately established, it would be reasonable to propose that the trait is highly heritable, probably in a dominant mode, as proposed by Tattersall and Fajans.

With such strong evidence of an inherited disorder the question is: what defect is inherited? The glucose tolerance curve clearly demonstrates that the condition can advance to severe diabetes. Taken in conjunction with the serum immunoreactive insulin responses and the calculated ratios and indices, it is abundantly clear that insulin secretion is deficient in response to glucose stimulation. In this respect the diabetes in no way differs from severe non-insulin-dependent diabetes in older adults and the conclusion that the patients inherited a defect in insulin secretion in response to glucose stimulation would appear self-evident. However, such a conclusion would be naive. Reaven has recently once again emphasized that in non-insulin-dependent diabetes severe glucose intolerance attenuates the insulin response, and this has been demonstrated in this study when the group was subdivided in terms of the severity of the disorder; the more severe diabetics had a more attenuated insulin response when it is considered that the mean fasting plasma glucose level was 12.3 mmol/l. These values are more than twice the mean value reported by Campbell and McKeechnie. Unfortunately the numbers approximating the desirable mass (12%) were too small for valid comparisons.

Data presented here therefore do not permit any conclusion as to whether the inherited defect is essentially peripheral or located in the islet cells. The fact that the evidence for a dominant type of inheritance is so strong argues in the first instance for a specific location of the defect rather than heterogeneity in the pathogenesis of the disorder. It may well be that NIDDDY could serve as a model to characterize pathogenetic aspects of non-insulin-dependent diabetes. As in non-insulin-dependent diabetes in older adults the patients tend to obesity; the insulin response is attenuated in the face of hyperglycaemia; it seems to be a progressive disorder in so far as glucose area correlates with the duration of diabetes although there seems to be some compensatory insulin response in that the insulin area did not correlate with the duration.

Future studies will deal with vascular complications and with familial age of onset.

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REFERENCES


**TABLE IV. PLASMA GLUCOSE AND SERUM INSULIN LEVELS (MEAN ± SEM) IN MODERATE (PLASMA GLUCOSE ≤ 12.8 mmol/l) AND SEVERE DIABETES (> 12.8 mmol/l)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Plasma glucose (mmol/l)</th>
<th>Serum insulin (μU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>0 min</td>
<td>(47)</td>
<td>(34)</td>
</tr>
<tr>
<td>60 min</td>
<td>17.23 ± 0.53</td>
<td>24.09 ± 0.68</td>
</tr>
<tr>
<td>120 min</td>
<td>18.45 ± 0.68</td>
<td>25.13 ± 0.74</td>
</tr>
<tr>
<td>180 min</td>
<td>16.46 ± 0.82</td>
<td>23.63 ± 0.87</td>
</tr>
</tbody>
</table>

* P < 0.001.
+ P > 0.05.