THE IMMUNOREACTIVE GROWTH HORMONE IN SERUM FROM PATIENTS WITH VARIOUS TYPES OF DIABETES MELLITUS

By Hans Yde

ABSTRACT

Employing a chromatographic method the immuno-reactive serum growth hormone was determined in 102 diabetics and 45 controls. The diabetic group consisted of 40 juvenile diabetics and 62 newly diagnosed untreated maturity-onset diabetics. 12 of the juvenile diabetics were newly diagnosed and untreated, while the remaining 28 were long-term diabetics. 33 of the maturity-onset diabetics were non-obese while 29 were obese. All the persons were investigated while fasting in the resting state before getting out of bed. All the groups of diabetics presented an elevated mean fasting serum growth hormone of the same order of magnitude. When the total group of 102 diabetics was analysed against the controls, and also when the 62 maturity-onset diabetics were analysed separately, a statistically significant elevation in the mean fasting serum growth hormone was obtained. This was not the case when the group of 40 juvenile diabetics were analysed separately.

In 10 maturity-onset diabetics the serum growth hormone response to oral glucose was found to be normal as compared to 13 controls.

Since the introduction of the radio-immunological assay for growth hormone, our knowledge about plasma growth hormone in health and disease has increased enormously.

In the healthy subject, plasma growth hormone has proved to have wide daily fluctuations. It has also been shown that oral glucose induces a suppression of plasma growth hormone followed by a secondary rise (Roth et al.)

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Hypoglycaemia produced by insulin, results in an increased plasma growth hormone level. The same is true for the intra-cellular hypoglycaemia induced by 2-deoxy glucose. Certain aminoacids, e.g. arginine (Knopf et al. 1965; Merimee et al. 1965), also influence plasma growth hormone. They induce a rise in the plasma growth hormone level one hour after iv administration.

Several other factors influence the plasma growth hormone concentration. Thus exercise is known to produce an increase which can be counteracted by glucose administration (Frantz & Rabkin 1965; Hunter et al. 1965, 1968); mental stress (Greenwood & Landon 1966; Schalch 1967; Baylis et al. 1968) and venepuncture (Copinschi et al. 1967) are also known to increase plasma growth hormone.

In a study of plasma growth hormone it is therefore essential to take these factors into account and standardize the state of the persons examined before blood sampling procedures are carried out. In previous studies on plasma growth hormone in diabetes mellitus no major abnormality was demonstrated, but the factors described above were not sufficiently taken into consideration.

We therefore found it worthwhile to re-evaluate the problem of serum growth hormone and diabetes mellitus by studying the fasting serum growth hormone level in a large group of control subjects and patients with various types of diabetes mellitus under strictly standardized conditions, in order to reduce the variation in serum growth hormone as much as possible. The serum growth hormone was also studied after oral glucose in smaller groups of control subjects and diabetics.

**MATERIAL AND METHODS**

**Controls:** The series consisted of 45 subjects (19 female and 26 male). The mean age ± SEM is indicated in Table 1. The group was composed of students and patients with minor physical disease, all having a normal fasting blood glucose, without fasting glucosuria and without diabetes mellitus in the nearest family. All these subjects were of normal weight, i.e. a weight less than 115% of mean weights for a normal Danish population aged 30-34 years (Secher 1934).

**Diabetics:** 102 diabetics were investigated. These consisted of 12 newly diagnosed, untreated juvenile diabetics, 28 insulin treated long-term diabetics with proliferative diabetic retinopathy, 62 newly diagnosed, untreated maturity-onset diabetics of whom 29 were obese and 33 were non-obese. 59 of the diabetics were female. Obesity was defined according to the definition mentioned above. The mean age ± SEM of the patients is indicated in Table 2.

**Procedures:** All the patients and control subjects were investigated during hospitalization after an overnight sleep in the fasting condition. Neither the controls nor the diabetics were allowed to leave bed the night before or during the investigation. The insulin treated diabetics received the last insulin injection 24 h before the investigation. Consequently none of them had any hypoglycaemia in the morning on
which the blood sampling took place. The blood glucose range was between 117 and 350 mg per 100 ml.

In 13 of the controls and 10 of the maturity-onset diabetics the serum growth hormone was followed during a glucose tolerance test (100 g of glucose dissolved in about 200 ml water flavoured with lemon juice). These tests were also made during admission to the department. The glucose was given between 7 and 9 a.m. Twelve blood samples were taken during the six hour test by means of an indwelling venous catheter inserted into a cubital vein.

Immediately after collection, the blood was kept at +4°C for one hour and then spun at room temperature for five minutes at 3000 r.p.m. in an ordinary laboratory centrifuge, after which the serum was stored at −20°C.

Serum growth hormone was determined radio-immunologically by a chromatographic method published elsewhere (Yde 1968).

Blood glucose was determined by the glucose oxidase method (Hugget & Nixon 1957).

RESULTS

Table 1 shows the mean concentration of serum growth hormone ± sem in the 45 non-obese controls, investigated in the fasting state, before getting out of bed after a nights sleepy. The group is divided into females and males. It appears from Table 1 that under these standardized resting conditions, the serum growth hormone concentration is of the same order of magnitude in male and female subjects.

Table 2 shows the mean serum growth hormone concentration ± sem in 102 diabetics of different types, studied under conditions identical with those of the controls. Table 2 also includes the P values obtained after statistical comparison with the control group.

The average fasting serum growth hormone (4.1 ng/ml ± 0.7) was higher in the 40 juvenile diabetics than in the controls, but the difference was not statistically significant. In the 12 newly diagnosed, untreated cases the mean fasting serum growth hormone value obtained was 4.9 ng/ml ± 1.4, while in

<table>
<thead>
<tr>
<th></th>
<th>Mean age ± SEM</th>
<th>Number</th>
<th>Mean GH ng/ml ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (♂)</td>
<td>39 ± 3</td>
<td>26</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>Female (♀)</td>
<td>36 ± 4</td>
<td>19</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>Total</td>
<td>38 ± 2</td>
<td>45</td>
<td>2.8 ± 0.5</td>
</tr>
</tbody>
</table>
Table 2.
Mean fasting and resting serum growth hormone in diabetics of different types.

<table>
<thead>
<tr>
<th>Type of diabetes</th>
<th>Mean age ± sem</th>
<th>Number</th>
<th>Mean GH ng/ml ± sem</th>
<th>( p^o )</th>
</tr>
</thead>
<tbody>
<tr>
<td>juvenile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>newly diagnosed</td>
<td>19 ± 4</td>
<td>12</td>
<td>4.9 ± 1.4</td>
<td>0.1 &gt; ( p &gt; 0.05 )</td>
</tr>
<tr>
<td>untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>long-term</td>
<td>31 ± 2</td>
<td>28</td>
<td>3.8 ± 0.7</td>
<td>0.5 &gt; ( p &gt; 0.2 )</td>
</tr>
<tr>
<td>total</td>
<td>28 ± 1</td>
<td>40</td>
<td>4.1 ± 0.7</td>
<td>0.2 &gt; ( p &gt; 0.1 )</td>
</tr>
<tr>
<td>maturity onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>obese</td>
<td>62 ± 2</td>
<td>29</td>
<td>4.1 ± 0.5</td>
<td>0.1 &gt; ( p &gt; 0.05 )</td>
</tr>
<tr>
<td>non-obese</td>
<td>62 ± 2</td>
<td>33</td>
<td>4.1 ± 0.6</td>
<td>0.1 &gt; ( p &gt; 0.05 )</td>
</tr>
<tr>
<td>total</td>
<td>62 ± 1</td>
<td>62</td>
<td>4.1 ± 0.4</td>
<td>0.05 &gt; ( p &gt; 0.025 )</td>
</tr>
<tr>
<td>Total</td>
<td>49 ± 2</td>
<td>102</td>
<td>4.1 ± 0.4</td>
<td>0.05 &gt; ( p &gt; 0.025 )</td>
</tr>
</tbody>
</table>

* The \( p \)-value obtained after statistical comparison with the controls.

the 28 long-term cases it was 3.8 ng/ml ± 0.7. Neither of these elevations was statistically significant.

The average serum growth hormone value obtained in the 62 maturity-onset diabetics was also higher than in the controls, and of about the same order of magnitude as in the juveniles. However, statistical calculations revealed a significant difference as compared to the control group. The two subgroups (obese and non-obese maturity-onset diabetics) similarly exhibited elevated mean fasting growth hormone values, but as appears from Table 2 the elevations were not statistical significant.

When the total group of all types of diabetics are analyzed against the controls, a significant serum growth hormone elevation is obtained.

No correlation could be demonstrated between the blood glucose and serum growth hormone in any of the groups of diabetics. As in the controls, no sex difference was obtained in the diabetic patients.

Table 3 shows the serum growth hormone values obtained in 10 patients with maturity-onset diabetes during a six hour oral glucose load. At the bottom of Table 3 the mean serum growth hormone ± sem is shown together with the mean serum growth hormone values obtained in 13 controls. No significant difference was found between the post-glucose values in the controls and the maturity-onset diabetics. This is also the case after dividing the maturity-onset diabetics into obese and non-obese patients. The pattern found in the individual patients is thus of the same type as that of the controls.
Table 3.
Serum growth hormone levels (ng/ml) during oral glucose loading in 10 maturity-onset diabetics and the mean response in 13 controls.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Weight %</th>
<th>0</th>
<th>1/4</th>
<th>1/2</th>
<th>3/4</th>
<th>1</th>
<th>1 1/2</th>
<th>2</th>
<th>2 1/2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>♂</td>
<td>&lt;115</td>
<td>0.5</td>
<td>0.5</td>
<td>0.8</td>
<td>1.0</td>
<td>1.4</td>
<td>&lt;0.5</td>
<td>0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>12.0</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>♂</td>
<td>&gt;115</td>
<td>1.4</td>
<td>1.5</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
<td>&lt;0.5</td>
<td>0.5</td>
<td>&lt;0.5</td>
<td>2.6</td>
<td>1.3</td>
<td>&lt;0.5</td>
<td>4.8</td>
</tr>
<tr>
<td>3</td>
<td>♂</td>
<td>&gt;115</td>
<td>17.0</td>
<td>4.0</td>
<td>7.2</td>
<td>5.3</td>
<td>5.9</td>
<td>3.5</td>
<td>5.9</td>
<td>4.8</td>
<td>14.6</td>
<td>--</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>4</td>
<td>♂</td>
<td>&lt;115</td>
<td>5.9</td>
<td>6.3</td>
<td>5.8</td>
<td>5.8</td>
<td>6.4</td>
<td>5.3</td>
<td>3.4</td>
<td>9.6</td>
<td>--</td>
<td>2.2</td>
<td>--</td>
<td>9.9</td>
</tr>
<tr>
<td>5</td>
<td>♂</td>
<td>&gt;115</td>
<td>2.2</td>
<td>2.2</td>
<td>1.0</td>
<td>1.3</td>
<td>0.5</td>
<td>0.7</td>
<td>1.0</td>
<td>11.3</td>
<td>3.4</td>
<td>&lt;0.5</td>
<td>2.1</td>
<td>2.7</td>
</tr>
<tr>
<td>6</td>
<td>♂</td>
<td>&gt;115</td>
<td>4.6</td>
<td>0.8</td>
<td>0.8</td>
<td>&lt;0.5</td>
<td>1.0</td>
<td>0.9</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>0.5</td>
<td>&lt;0.5</td>
<td>1.6</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>7</td>
<td>♂</td>
<td>&gt;115</td>
<td>3.0</td>
<td>1.6</td>
<td>&lt;0.5</td>
<td>8.8</td>
<td>8.9</td>
<td>8.6</td>
<td>2.4</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>8</td>
<td>♂</td>
<td>&gt;115</td>
<td>&lt;0.5</td>
<td>--</td>
<td>0.8</td>
<td>--</td>
<td>3.0</td>
<td>1.2</td>
<td>3.4</td>
<td>&lt;0.5</td>
<td>--</td>
<td>7.6</td>
<td>&lt;0.5</td>
<td>1.2</td>
</tr>
<tr>
<td>9</td>
<td>♀</td>
<td>&lt;115</td>
<td>&lt;0.5</td>
<td>2.1</td>
<td>1.2</td>
<td>--</td>
<td>1.4</td>
<td>1.6</td>
<td>1.6</td>
<td>1.4</td>
<td>--</td>
<td>0.8</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>10</td>
<td>♀</td>
<td>&lt;115</td>
<td>&lt;0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>--</td>
<td>--</td>
<td>3.2</td>
<td>2.9</td>
<td>2.1</td>
<td>1.8</td>
<td>1.4</td>
<td>2.9</td>
<td>0.8</td>
</tr>
</tbody>
</table>

| Mean ± SEM | 3.4 ± 2.0 | 2.1 ± 0.7 | 1.8 ± 0.8 | 3.3 ± 1.2 | 3.2 ± 0.9 | 2.5 ± 0.6 | 2.1 ± 1.3 | 3.3 ± 1.9 | 3.8 ± 0.8 | 1.3 ± 0.6 | 3.5 ± 1.2 | 3.1 ± 1.2 |

Controls n = 13

| Mean ± SEM | 2.2 ± 0.6 | 3.0 ± 1.4 | 1.3 ± 0.5 | 1.4 ± 0.6 | 1.4 ± 0.6 | 2.0 ± 0.5 | 2.1 ± 0.8 | 2.0 ± 0.7 | 4.1 ± 0.8 | 5.4 ± 2.2 | 4.5 ± 1.7 | 4.5 ± 1.1 |
DISCUSSION

It appears from the results obtained in the present study that the mean fasting serum growth hormone is significantly elevated in a large group of patients with diabetes mellitus. The mean serum growth hormone values obtained in the maturity-onset and juvenile type of diabetics are both equally elevated; however, on analysing the individual groups, only the mean value obtained in the maturity-onset type is statistically significant (i.e. \( P < 0.05 \)).

It has been shown that exercise results in elevation of plasma growth hormone. This, however, could not be the reason for the elevated serum growth hormone demonstrated in the present study, since all the control subjects as well as the diabetics, were investigated in the resting and fasting state before getting out of bed. Hypoglycaemia is also known to induce a high plasma growth hormone (Roth et al. 1963a,b). As none of our patients had a low blood sugar at the time of examination this could not be the reason for our findings.

Plasma growth hormone has been shown not to be influenced by age in adult subjects (Glick et al. 1965); consequently the difference in the mean age between our control subjects and the diabetic patients cannot be the explanation for the elevated serum growth hormone value found.

Investigating newly diagnosed untreated juvenile diabetic children, Parker et al. (1968) and Baker et al. (1967) found a normal average fasting plasma growth hormone. By measuring the serum growth hormone every 30 minutes for 24 h in 5 somewhat older patients with newly diagnosed untreated juvenile diabetes Johansen & Hansen (1969) found elevated mean values at all the times examined, including the fasting state.

In 1966 Powell et al. stated that long-term diabetics had a normal fasting plasma growth hormone, but no control findings were included in the report. Franchimont & van Cauwenberge (1966) reported an increase in plasma growth hormone in 5 patients with long-term diabetes examined in the fasting state. This increase might have been spurious and caused by hypoglycaemia.

Reports on plasma growth hormone values in maturity-onset diabetics are more numerous than in juvenile diabetics, but only one of the investigations was performed on patients in the basal state. Glick et al. (1963, 1965) found normal plasma growth hormone values in adult diabetics studied 1–3 h after a meal as well as in the fasting state, but no information was given concerning the diabetic state nor whether the patients were treated or untreated. Hunter et al. (1966) and Merimee et al. (1966) studying fasting plasma growth hormone in newly diagnosed untreated diabetics also found normal values. Tchobroutsky et al. (1967) have avoided muscular work by investigating subjects before getting out of bed in the fasting state, as was done in the present study. They found a tendency to a higher plasma growth hormone concentra-
tions in treated diabetics. In the present study we found a significant elevation in the mean serum growth hormone concentration in the total group of diabetics investigated as well as in the maturity-onset diabetics. The discrepancy between the results obtained in previous examinations and the present study could have been caused by the susceptibility of plasma growth hormone to extrinsic factors which had not been taken into account in earlier studies.

In contrast to Hunter et al. (1966) we found, identical serum growth hormone concentrations in obese and non-obese subjects. As lean people are more prone to react with bursts of growth hormone during minor exercise than overweight subjects, this finding might have been the result of our basal experimental conditions.

The mean serum growth hormone concentration obtained for the maturity-onset diabetics in the present study during oral glucose loading was not different from that obtained in the control subjects. This finding is in agreement with earlier reports by Hunter et al. (1966) and Yalow et al. (1965). Danowski et al. (1968) reported a blunted plasma growth hormone response to oral glucose in 9 subjects presumed to be diabetic.

Recently Yde (1969) found an early hyper-response of serum growth hormone in juvenile diabetics after oral glucose loading. Johansen & Hansen (1969) reported abnormal serum growth hormone concentrations throughout the day in juvenile diabetics and Hansen (1969, personal communication) found an abnormal serum growth hormone response to exercise in juvenile diabetics. The results presenting in the present study showing elevated mean serum growth hormone concentrations in diabetics together with the above mentioned reports points to an abnormal growth hormone regulation in the disease diabetes mellitus. This might be post or propter hoc but it is worth mentioning that an abnormal growth hormone regulation has been demonstrated even in prediabetics (Boden et al. 1968; Sonksen et al. 1968).

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