REVERSAL BY INSULIN TREATMENT OF ABNORMAL GROWTH HORMONE PATTERN IN NEWLY DIAGNOSED DIABETES MELLITUS

By

ABSTRACT

The effect of insulin therapy on growth hormone secretion was studied in five newly diagnosed young insulin-dependent diabetic men. All showed a markedly abnormal pattern of secretion immediately prior to insulin therapy and following "normalization" of the blood glucose there was a significant fall in plasma growth hormone levels after a period of one to two months though these were still considerably elevated above the normal control range. These findings lend support to the view that the abnormal growth hormone secretion observed in diabetes may be the consequence rather than the cause of the disordered carbohydrate metabolism.

The role of increased growth hormone (GH) secretion in the pathogenesis of diabetes mellitus has continued to be debated (Cerasi & Luft 1970) since the initial observations of Young (1939) who postulated that hypersecretion of GH might be the cause of diabetes in man. In a study from Denmark (Hansen & Johansen 1970) untreated juvenile-onset diabetics showed elevated GH levels when compared with non-diabetic controls on the basis of 24 hour profiles
which were designed to provide a standardized procedure simulating normal life. The aim of the present study was to show the possible effect of initial insulin treatment on the abnormal GH pattern in newly diagnosed diabetics and the period required for the reversal of these changes.

MATERIALS AND METHODS

Five newly diagnosed insulin-dependent male diabetics aged between 16 and 27 years (mean age 20) were studied before and after insulin treatment. All subjects were underweight, 73 % to 94 % standard weight (mean 87 %) when diagnosed and all gave a history of classical symptoms. None of the patients was significantly ketoacidotic at diagnosis: all had plasma bicarbonate values exceeding 18.0 mEq./l.

The initial period of study (Period 1) was undertaken at the time of diagnosis. Immediately thereafter, all patients were started on Soluble and Isophane (NPH) insulins injected twice daily before breakfast and before the main evening meal. Approximately one month later all subjects were re-admitted for one day (Period 2) for repetition of the GH studies. Insulin therapy was continued during this second period. In the two patients (Nos. 4 and 5) in whom the GH secretory response was still markedly abnormal (vide infra) the same regimen was again repeated (Period 3) after a further month's treatment with insulin.

Table 1 shows the simulated daily activity followed in the three periods. Each patient was studied for 16 hours commencing at 07.00 hours after an overnight fast. The regimen consisted of three main meals, two small interval snacks and two fifteen minute spells of brisk walking at 17.00 and 20.30 hours. The subjects remained recumbent between meals and the spells of exercise; smoking was prohibited. The diet contained 2200 calories and consisted of approximately 240 g of carbohydrate, 80 g of protein and 97 g of fat.

Blood samples were withdrawn by venipuncture at half-hourly intervals for blood glucose and plasma GH determinations. The samples for blood glucose measurement were stored in fluoride oxalate tubes at 4°C and determined on the same or following day by Autoanalyser. Plasma obtained by centrifugation of heparinized blood was stored at −20°C for GH immunoassay using the method of Hunter & Greenwood (1964) but utilizing a double antibody separation (Hunter 1972).

Table 1.
Regimen for the 16 hour period of simulated daily activity.

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Composition</th>
</tr>
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<tbody>
<tr>
<td>07.00</td>
<td>First sample withdrawn</td>
<td></td>
</tr>
<tr>
<td>08.00</td>
<td>Breakfast (B): Protein 21 g, Fat 34 g, CHO 65 g</td>
<td></td>
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<tr>
<td>10.30</td>
<td>Mid-morning snack (S): Protein 6 g, Fat 8 g, CHO 23 g</td>
<td></td>
</tr>
<tr>
<td>13.00</td>
<td>Lunch (L): Protein 32 g, Fat 16 g, CHO 68 g</td>
<td></td>
</tr>
<tr>
<td>17.00</td>
<td>Brisk 15 minute walk</td>
<td></td>
</tr>
<tr>
<td>19.00</td>
<td>Dinner (D): Protein 23 g, Fat 31 g, CHO 60 g</td>
<td></td>
</tr>
<tr>
<td>20.30</td>
<td>Brisk 15 minute walk</td>
<td></td>
</tr>
<tr>
<td>22.00</td>
<td>Late night snack (S): Protein 6 g, Fat 8 g, CHO 23 g</td>
<td></td>
</tr>
<tr>
<td>23.00</td>
<td>Last sample withdrawn</td>
<td></td>
</tr>
</tbody>
</table>
The normal diurnal pattern of plasma GH concentration was obtained from a previous study of seven healthy non-obese adult males, aged 25 to 48 years, using the same hormone assay technique and laboratory (Hunter et al. 1966).

RESULTS

The pre- and post-treatment plasma GH profiles in the five diabetic subjects are shown in Fig. 1, which also shows the range of GH secretion in the seven

![Fig. 1.](image)

Plasma growth hormone (GH) profiles in five newly diagnosed insulin-dependent diabetic males before and after treatment. (Patients 1–3, one month after treatment; patients 4 and 5 two months after treatment. Open circles represent pre-treatment GH levels; closed circles represent post-treatment GH levels). Times of meals indicated by arrows. Periods of brisk walking occurred at 17.00 and 20.30 hours. Hatched area represents the range of GH secretion in seven male control subjects.
Table 2.
Mean and standard deviation of half-hourly values of blood glucose and plasma GH values of diabetic subjects.

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Blood glucose mg/100 ml</th>
<th>Plasma growth hormone ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 1</td>
<td>Period 2</td>
</tr>
<tr>
<td>1</td>
<td>245 ± 57</td>
<td>156 ± 36</td>
</tr>
<tr>
<td>2</td>
<td>276 ± 60</td>
<td>105 ± 49</td>
</tr>
<tr>
<td>3</td>
<td>282 ± 43</td>
<td>173 ± 52</td>
</tr>
<tr>
<td>4</td>
<td>308 ± 47</td>
<td>149 ± 48</td>
</tr>
<tr>
<td>5</td>
<td>244 ± 91</td>
<td>86 ± 43</td>
</tr>
</tbody>
</table>
adult male controls during normal diurnal activity, from previously published data (Hunter et al. 1966). In these control subjects plasma GH was generally below 0.5 ng/ml while early post-absorptive peaks not exceeding 3.0 ng/ml were found. Table 2 shows the mean and standard deviation of the half-hourly values of the blood glucose and plasma GH concentration. The blood glucose values in all subjects were considerably elevated before commencing insulin therapy and returned towards normal in every case following one month’s treatment. The GH levels in all patients at diagnosis were clearly abnormal; while the main mixed meals almost invariably suppressed GH secretion this suppression was more briefly maintained and the rebound rises were more frequently seen and were markedly larger than in the controls.

Following the first month of treatment with insulin there was a significant fall of the blood glucose values in every case ($P < 0.001$). This was associated with a significant fall in the mean plasma GH concentration ($P < 0.001$) and a return towards the normal pattern in three of the subjects (1, 2 and 3). In the remaining two patients (4 and 5, not illustrated) there was no significant fall in the mean plasma GH levels ($P > 0.05$) following the first month of treatment despite the relative normalization of the blood glucose profile. In both these latter patients the mean GH levels, however, became less abnormal ($P < 0.05$ and $P < 0.001$ respectively) following a further month’s insulin therapy, and these results are represented in Fig. 1.

Immediately following both spells of brisk walking there was a tendency to an increased GH response which became less following the improved diabetic control.

**DISCUSSION**

Though abnormalities in growth hormone secretion have been frequently observed in diabetes mellitus, especially at diagnosis, these are thought to be secondary to the metabolic abnormality of the uncontrolled disorder and it is presently believed that GH probably does not play a primary role in the pathogenesis of diabetes (Luft & Cerasi 1970). Other workers, however, have failed to demonstrate increased GH levels in newly diagnosed untreated diabetics. Generally these studies have not included the measurement of GH levels in response to normal daily stimuli. For example Theodoridis et al. (1971) studied the response to oral glucose loading and Baker et al. (1969) used the intravenous arginine infusion test. Body weight might also account for the variation in GH concentration reported by different observers since in the presence of obesity there is a blunting of the secretory response (Rabinowitz 1970).
The present study was designed to show the effect of insulin treatment, with improved control, on the abnormal GH levels in newly diagnosed diabetics. The results confirm the findings of Hansen & Johansen (1970) who studied newly diagnosed untreated insulin-dependent (juvenile onset) diabetics. They found raised mean levels of serum GH which fluctuated considerably over a simulated 24 hour "daily life" period and showed more frequent and higher peaks than in non-diabetic controls. These same patients were not studied following insulin treatment. In a further study by the same investigators, however (Johansen & Hansen 1971) good control by insulin therapy for 9-10 months had resulted in significantly lower serum GH concentrations, while in two poorly controlled patients, with diabetes of longer duration, better control did not alter the abnormal GH levels. Molnar et al. (1972) found that improved control in unstable insulin taking diabetics which was achieved with an intensified insulin regimen, though resulting in a significant reduction in the mean diurnal blood glucose values, did not significantly alter the GH levels. The present study suggests that although blood glucose may show near normalization more rapidly a minimum period of 1-2 months of insulin therapy is probably required for a significant reduction in the plasma GH levels.

Taylor et al. (1969) and later Lipman et al. (1972) suggested that the elevated plasma GH levels in insulin-dependent diabetics may not necessarily be due to increased anterior pituitary secretion but rather to decreased metabolic clearance rate of GH. These investigators have postulated an as yet undefined defect in hepatic GH clearance, the liver being the major organ responsible for the clearance of GH from the plasma in man. The difference in GH levels between the normal and the insulin-dependent patients, however, seemed to be too great to be accounted for in this way.

It can be seen from the results of the present study that though there was ultimately, after 1-2 months, a significant fall of GH in all five patients when well controlled, the plasma GH levels nevertheless were still considerably greater than in the control subjects. The residual elevation of plasma GH is presumably involved in the metabolic adjustment (increased fat mobilization) from the continuing inability to utilize carbohydrate normally. Lundbæk et al. (1970) have postulated that these abnormal GH levels may have a role in the development of diabetic angiopathy but whether the complications of diabetes are a consequence of this particular metabolic disturbance or are the result of direct actions of GH unrelated to these changes remains to be seen.

REFERENCES


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