Abstract

Objective: To study plasma concentrations of insulin-like growth factor-I (IGF-I) in adults with type 1 diabetes (IDDM) in comparison with a reference population, and the influence of glycaemic control, dose of insulin, and sex on the concentration of circulating IGF-I in IDDM.

Design and methods: Patients with type 1 diabetes were recruited consecutively from our outpatient diabetes unit. In all, 79 men and 55 women aged 20–60 years with a disease duration $6$ years (range 6–51 years) took part in the study. A reference population of 80 men and 83 women aged 20–60 years was randomly obtained from the population registry. IGF-I was measured with radioimmunoassay after acid–ethanol extraction.

Results: Mean $\pm$ S.D. values of IGF-I were lower in patients with diabetes (146 $\pm$ 66 $\mu$g/l) than in controls (238 $\pm$ 83 $\mu$g/l, $P<0.001$). Those with diabetes had lower IGF-I concentrations in all age groups and the differences were highly significant in all decades except in women aged 50–59 years. IGF-I was negatively correlated with age in patients and controls. No correlation was found between IGF-I and glycaemic control measured as haemoglobin A1c (HbA1c) in the patients. IGF-I was positively associated with the dose of insulin/kg body weight in male patients independently of age, HbA1c and body mass index ($P<0.03$), but not in female patients ($P=0.14$).

Conclusions: Our data show that IGF-I concentrations are low in adult patients with type 1 diabetes with a disease duration $\geq$ 6 years, independently of glycaemic control. This suggests that subcutaneous insulin substitution is inadequate to normalize circulating IGF-I concentrations in patients without endogenous insulin secretion.

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Introduction

Insulin-like growth factor-I (IGF-I) mediates growth effects of growth hormone (GH) in childhood and anabolic effects of GH on muscle, skeleton and other tissues in adult man (1). The plasma concentrations of IGF-I are mainly regulated by growth hormone (GH), but are also affected by insulin and nutrients (2–6). Low plasma levels of IGF-I are found in adolescent patients with type 1 diabetes (7–11) and have also been reported in adult patients with IDDM (12–15). A negative relationship between glycaemic control and plasma concentrations of IGF-I has been found in children and adolescents with diabetes (7, 16, 17). However, there are few studies on the relationship between glycaemic control and plasma concentrations of IGF-I in adult patients with type 1 diabetes. A negative relationship between glycaemic control and circulating IGF-I has been shown by some investigators (13, 14, 18) but not by others (19, 20). In adult patients with type 1 diabetes with good glycaemic control and without endogenous production of insulin, the plasma concentrations of free insulin are normal or increased in the fasting state and between meals, whereas meal-related insulin peaks are low compared with those in non-diabetic control individuals (21). In man, circulating IGF-I is considered to be produced mainly by the liver (1). Even when the peripheral plasma concentrations of insulin are close to the normal range, the intraportal liver concentrations are considerably less than physiological concentrations (22, 23). Indeed intraperitoneal or intraportal insulin delivery has been found to be more effective than subcutaneous infusion of insulin to increase plasma IGF-I concentrations in adult patients with type 1 diabetes, indicating that portal insulin concentrations are of importance for circulating IGF-I concentrations in patients with this condition (18, 20). The objective of our study was to compare plasma...
concentrations of IGF-I in a large sample of adult patients with type 1 diabetes, and little or no endogenous insulin secretion and in a reference population. We also wanted to study the relationships of circulating IGF-I concentrations with glycaemic control, dose of insulin, body mass index (BMI) and sex in patients with type 1 diabetes.

**Participants and methods**

**Participants**

Patients with type 1 diabetes were recruited consecutively from our outpatient diabetes unit (Table 1). Patients with serum creatinine concentrations greater than 120 µg/l (reference ranges: men 70–115 and women 55–100 µg/l) or albuminuria greater than 1 g/day were not included in the study. In all, 79 men and 55 women aged 20–60 years who had a disease duration ≥6 years (range 6–51 years) took part in the study. The patients were diagnosed according to the 1985 WHO criteria (24). Most patients were receiving insulin treatment with regular insulin before meals three times per day and intermediate-acting (NPH or Lente) insulin at night. Only a few patients injected intermediate acting or mixed intermediate acting and regular insulin twice daily. Fifteen patients (nine men and six women) had microalbuminuria of between 30 and 300 mg/day and six patients (four men and two women) had albuminuria of between 300 and 670 mg/day. A reference population of 83 women and 80 men aged 20–60 years, evenly distributed in each 10-year interval, was randomly obtained from the population registry in the community of Linköping. Control subjects with treated hypertension or those who were pregnant were excluded. The participation rate was 67% of those invited (25) (Table 1). Of the 55 women patients with diabetes, two used oral contraceptives and two were receiving postmenopausal replacement therapy with oestrogens; of the 83 women control individuals, eight used oral contraceptives and 11 were receiving postmenopausal replacement therapy with oestrogens (nine oral and two transdermal). Body weight was measured with the individual in light clothing and without shoes. BMI was calculated according to the formula: mass (kg) divided by height (m) squared.

**Ethics**

The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. The controls and patients with diabetes were informed about the purpose of the study and gave their informed consent to participate.

**Laboratory analyses**

Venous blood sampling was performed in the reference population in the fasting state between 0800 and 0900 h. In the diabetic population, venous blood sampling was performed in the non-fasting state from 0800 to 1200 h. We measured circulating IGF-I in a group of 11 patients with type 1 diabetes at 0800 h in a fasting state, and in the non-fasting state at 1200 h and 1530 h. No significant difference was found between the three IGF-I measurements (Table 2).

Serum IGF-I was measured with a commercial kit from Nichols Institute (San Juan, Capistrano, CA, USA), by radioimmunoassay (RIA) after acid–ethanol extraction of IGF-I from its binding proteins. The assay was performed according to the manufacturer’s procedure. Intra- and interassay coefficients of variation for serum IGF-I were 1.5% and 13% respectively. Sera had been kept frozen at −20°C for up to 3 years until required for analysis of IGF-I. Haemoglobin A1c (HbA1c) was measured with HPLC (reference range 3.2–5.6%), interassay coefficient of variation 3%. Creatinine concentrations in plasma and albumin in urine were analysed with our routine hospital methods.

**Statistical analysis**

Statistical calculations were made using a Macintosh personal computer and StatView 4.5 software. Baseline

**Table 1 Clinical characteristics of the participants. Data are means±s.d.**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th></th>
<th>Controls</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>80</td>
<td>55</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>38±10</td>
<td>37±9</td>
<td>40±12</td>
<td>41±12</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>25±2.9</td>
<td>24.2±3.2</td>
<td>25.2±3.5</td>
<td>23.9±3.5</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>180±7.3</td>
<td>164±5.8</td>
<td>179±7</td>
<td>167±7</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>82±12</td>
<td>66±9</td>
<td>80±11</td>
<td>66±11</td>
</tr>
<tr>
<td><strong>Diabetes duration (years)</strong></td>
<td>22±11</td>
<td>22±10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>7.8±1.2</td>
<td>7.5±1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin dose (U/kg per day)</strong></td>
<td>0.72±0.21</td>
<td>0.65±0.19</td>
<td></td>
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</tr>
</tbody>
</table>

*P < 0.03 for the difference in age between female patients and female controls.
Table 2 Variations in plasma IGF-I concentrations measured in 11 diabetic patients (five men and six women) during the day. Data are means ± s.d.

<table>
<thead>
<tr>
<th>Time of sampling (h)</th>
<th>0800</th>
<th>1200</th>
<th>1530</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (µg/l)</td>
<td>176±99</td>
<td>178±105</td>
<td>180±93</td>
</tr>
</tbody>
</table>

No significant differences were found between the three measurements.

Clinical characteristics are presented as the means ± s.d. Differences between groups were tested with Student’s unpaired two tailed t-test or with analysis of variance (ANOVA). Multiple regression analysis was used to test possible explanatory variables affecting the IGF-I concentration in plasma. Differences of P ≤ 0.05 were considered significant.

Results

Plasma concentrations of IGF-I for all ages and both sexes were 146±66 µg/l in patients with type 1 diabetes and 238±83 µg/l in controls (P < 0.0001). IGF-I concentrations in men and women with type 1 diabetes were 135±63 and 162±68 µg/l respectively (P < 0.02). In male and female controls the IGF-I concentrations were 235±76 and 240±89 µg/l respectively (P = 0.72). The diabetic population had significantly lower IGF-I concentrations in all age groups (Fig. 1). When the participants were divided into groups according to sex, the difference in IGF-I concentrations did not reach statistical significance in female patients aged 50–59 years (n = 6). IGF-I was negatively correlated with age in male patients (r = −0.54), female patients (r = −0.36), male controls (r = −0.55) and female controls (r = −0.57). No correlation was found between IGF-I and glycaemic control, measured as HbA1c, in the total patient population (Fig. 2) or after calculation separately for men and women. Exclusion of the 21 patients with micro- or macroalbuminuria, or calculations excluding female patients receiving oestrogen therapy did not influence the relation between IGF-I and glycaemic control. The dose of insulin did not differ between male and female patients after correction for body weight (Table 1). IGF-I correlated positively with the dose of insulin corrected for body weight in male patients (P < 0.0001), but not in female patients (P = 0.77) (Fig. 3). Exclusion of the four patients receiving oestrogen therapy did not change the relation between IGF-I and the dose of insulin. IGF-I correlated negatively with BMI in male controls (P < 0.03), but no correlation was found in female controls or in female or male patients with type 1 diabetes. In multiple regression analysis with IGF-I as dependent factor and age, HbA1c, BMI and dose of insulin/kg body weight as independent factors, age remained negatively associated with IGF-I (P < 0.0001 and P < 0.004 in male and female patients respectively), and the dose of insulin corrected for body weight remained positively associated with IGF-I in male patients (P < 0.03), but not in women (P = 0.14).

Discussion

We found that adult patients with type 1 diabetes had low plasma concentrations of IGF-I that were not correlated to HbA1c. Our intention was to study patients without endogenous insulin production. Many patients with type 1 diabetes have a residual insulin secretion during the first years after diagnosis, but after 5 years the majority of patients are C-peptide negative (26). We therefore excluded patients with a duration of diabetes less than 6 years. Low IGF-I concentrations have previously been found in adult type 1 diabetes of long
duration, compared with those in non-diabetic controls (12–15, 27, 28). IGF-I correlates negatively with age in healthy individuals (29, 30). In our study, as in other studies, a negative correlation of IGF-I with age was found in adult patients with type 1 diabetes (13–15). The accumulated data strongly suggest that adult patients with type 1 diabetes without endogenous insulin production have low plasma concentrations of IGF-I, in comparison with non-diabetic controls.

There is little information in the literature on the relationship between glycaemic control and circulating IGF-I in adult patients with type 1 diabetes of long duration. We found low IGF-I in plasma independently of the HbA1c concentrations. In a large patient population, Dills et al. (14) found a very weak negative correlation ($r \approx -0.09$, $P < 0.05$) between IGF-I and glycated haemoglobin in patients with diabetes of long duration. Tan & Baxter (13) also found a negative correlation between IGF-I and HbA1c in diabetic patients younger than <50 years, but not in those older than 50 years, in a study in which the duration of the patients’ diabetes was not given. In two other studies reporting low IGF-I concentrations in large samples of patients, no information was given regarding circulating IGF-I concentrations in relation to HbA1c (12, 15). In contrast, in diabetic ketoacidosis there are reports of very low IGF-I concentrations, which were increased by insulin treatment, indicating that IGF-I concentrations are affected by severe metabolic decompensation (31, 32). Taken together, these data indicate that subcutaneous insulin substitution only partly restores the circulating concentrations of IGF-I in patients with type 1 diabetes of long duration.

There are several possible explanations for the low IGF-I concentrations in longstanding type 1 diabetes. Insufficient portal concentrations of insulin can cause hepatic GH resistance, resulting in decreased hepatic IGF-I production and impaired negative feedback of IGF-I on GH secretion, causing hypersecretion of GH (33). Hanaire-Broutin et al. (20) found that treatment of C-peptide negative patients with type 1 diabetes using intraperitoneal, but not subcutaneous, infusion of insulin nearly normalized plasma IGF-I without any change in HbA1c. In newly diagnosed young adult patients Shisko et al. (18) found that intraportal, but not subcutaneous, infusion of insulin normalized plasma IGF-I. However, in the latter study no data were given concerning endogenous production of insulin. Another explanation for low IGF-I concentrations in patients with type 1 diabetes could be increased elimination as a result of proteolysis of IGFBP-3 or increased excretion of IGF-I by the kidneys as a result of diabetic nephropathy (34). However, in normoalbuminuric patients, IGFBP-3 proteolysis is not increased (34, 35) and in our study we found no difference in IGF-I concentrations in patients with or without albuminuria. The available data thus suggest insufficient portal concentrations of insulin as the most probable cause of low plasma IGF-I in adult patients with type 1 diabetes of long duration. This explanation is also in accordance with our observation of a lack of correlation between circulating IGF-I and glycaemic control.

As IGF-I was analysed in the non-fasting state in the diabetes group and in the fasting state in the control population, we investigated variations in IGF-I concentrations during the day in a group of diabetic patients. We found no significant difference in IGF-I concentrations in the fasting state compared with the non-fasting state, which is in concordance with the findings of the study by Crosby et al. (27). We found a positive correlation between the injected dose of insulin and IGF-I concentrations in male patients independently of body weight, but no such correlation was found in the female patients. Jehle et al. (12) also found a positive correlation between the dose of insulin and IGF-I, but did not calculate data separately according to sex. Although there could be a sex-specific difference in the physiological effect of insulin on the IGF-I-generating capacity, others (14) did not find any difference in total IGF-I concentrations between male and female patients with diabetes or male and female controls.
The clinical significance of the low IGF-I concentrations found in patients with type 1 diabetes is at present unclear, but there are possible negative effects. IGF-I has anabolic effects on muscle, skeleton and other tissues, and is also important for carbohydrate metabolism: treatment with IGF-I subcutaneously has, in short-term trials, reduced insulin requirements (36). Very low IGF-I concentrations resulting from GH deficiency are associated with impaired muscle function and disordered bone metabolism (37). Musculoskeletal problems also occur in diabetic patients (38–40). In addition, decreased bone mineral content in female patients with type 1 diabetes (12) and increased risk of hip fracture in patients with type 1 diabetes or type 2 diabetes of long duration has been reported (41).

In conclusion, our data show that IGF-I in plasma are low and independent of glycaemic control in patients with type 1 diabetes of long duration. This suggests that subcutaneous insulin substitution is inadequate to normalize circulating IGF-I concentrations in patients without endogenous insulin secretion.

Acknowledgements

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