Growth hormone and insulin-like growth factor regulate insulin-like growth factor-binding protein-1 in Laron type dwarfism, growth hormone deficiency and constitutional short stature

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Insulin-like growth factors (IGFs) mediate the effects of growth hormone (GH), and the insulin-like growth factor-binding proteins (IGFBPs) modulate the actions of IGFs in tissues. We studied the circulating levels of IGFBP-1 in 6 children and 9 adults with Laron type dwarfism (LTD), in 11 children and 21 adults with growth hormone deficiency (GHD), and in 8 children with constitutional short stature. Compared with the situation in healthy children, the basal serum IGFBP-1 concentration was 5.4-fold higher in LTD children, 4.1-fold higher in GHD children, and 3.8-fold higher in children with short stature (p<0.02 vs controls in all groups). In adult patients with multiple pituitary hormone deficiency (MPHD), the IGFBP-1 concentration was 2-fold elevated, but it was normal in adult LTD patients. Intravenous (N = 10) or subcutaneous (N = 9) administration of IGF-I (75 µg·kg⁻¹ and 150 µg·kg⁻¹, respectively) in LTD children resulted in a rapid 50–60% fall in serum insulin (p<0.02), a decline in blood glucose and a concomitant 40–60% rise of IGFBP-1 levels (p<0.05). Treatment for seven days with IGF-I (150 µg·kg⁻¹·d⁻¹) resulted in a decrease by 34% and 44% of serum IGFBP-1 level in two out of three children with LTD. After prolonged GH therapy, the IGFBP-1 level fell in GHD children by 29% (p<0.05), in GHD adults by 52% (p<0.02) and in children with constitutional short stature by 17% (p<0.02). IGFBP-1 and insulin concentrations were inversely related in patients with GHD (r = –0.66, p<0.001) or with LTD (r = –0.57, p<0.05). Our data suggest that: (a) increased IGFBP-1 concentration in LTD, GHD and constitutional short children may, at least in part, be accounted for by an IGF-I deficiency; (b) both the rise in IGF-I and a fall in insulin contributed to the rise in IGFBP-1 after acute IGF-I administration; (c) prolonged IGF-I or GH treatment causes a persistent decline in IGFBP-1 concentration. In conclusion, IGF-I and GH may regulate IGFBP-1 secretion either directly or via insulin.

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Laron type dwarfism (LTD) (1, 2) is a hereditary disease due to a defect in GH receptors (3). In some patients the molecular defect is in the extracellular part of the GH receptor (4, 5), which is identical in structure to the GH-binding protein (6) and thus is absent in most LTD patients (7). These defects prevent any GH activity, including the generation of IGF-I (8).

The aim of the present study was to study the relationship between IGFBP-1, IGF-I and GH in extreme clinical conditions. We determined the circulating levels of IGFBP-1 in patients with LTD, growth hormone deficiency (GHD), and in children with growth retardation without GHD (e.g. constitutional short stature). In addition, we investigated the acute effects of IGF-I administration on serum insulin and IGFBP-1 concentrations, as well as the influence of prolonged IGF-I and GH treatments on serum IGFBP-1 levels.

Subjects

Patients with LTD (N = 15) included six children (4 boys, 2 girls) and nine adults (4 M, 5 F). Patients with GHD (N = 32) consisted of 11 children (7 boys, 4 girls). Six of them had an isolated growth hormone deficiency (IGHD) and five had multiple pituitary hormone deficiencies (MPHD) including GHD. A baseline sample for the IGFBP-1 determination was available in 9 patients with IGHD and 12 patients with MPHD. The effect of IGF-I therapy was examined in 15 adult GHD patients. Children with constitutional growth retardation included 8 boys whose height was 2 sd or more below the 50th centile. They were non-obese (skinfolds <10 mm), their bone age was retarded by two years or more, and all had a normal plasma GH response (>0.47 pmol/l) to exercise and/or to pharmacological stimuli. Healthy
controls (N = 43) included 20 children (9 prepubertal and 11 pubertal) and 23 non-obese adults (18M, 5F). All the subjects were investigated at the Institute of Pediatric and Adolescent Endocrinology, Beilinson Medical Center, Israel, except for the healthy adult controls, who were studied at the Second Department of Medicine, University of Helsinki, Finland. The pertinent clinical data of all the subjects are given in Table 1.

Study on acute effects. This study was performed on the LTD patients only. IGF-I (FK-780 Lot 137889 K, Fuji-sawa Pharmaceutical Co, Osaka, Japan) was given either as an iv bolus (75 μg·kg−1) in 10 LTD children, or subcutaneously (150 μg·kg−1) in 9 LTD children. Samples for serum IGFBP-1 and insulin measurements were taken in the basal state and as shown in Figs. 2 and 3. All the blood samples in this and the other studies were taken in the morning after an overnight (8–10 h) fast.

Chronic treatment. Three groups of patients were studied. Group 1: 15 LTD patients (6 children, 9 adults) received a sc injection of IGF-I for seven days at a dose of 120–150 μg·kg−1·d−1, and the blood samples were taken before and 24 h after the previous injection (9).

Group 2: Six children with GHD were treated with pituitary-extracted human GH (Grom, Serono, Switzerland) in a dose of 0.3–0.4 U·kg−1·week−1 divided into three weekly subcutaneous injections given in the evening. Blood samples were drawn in the fasting state after one or two weeks of treatment, in the morning 9–10 h after the previous injection. Fifteen adult GHD patients received biosynthetic recombinant human GH (Humatrope, Lilly, UK) 0.6 U·kg−1·week−1 divided into six subcutaneous injections administered in the evening. Fasting blood samples were taken before and during treatment (median 3 months; range 5 days to 1 year), 8–10 h after the previous injection.

Group 3: Eight constitutionally short children were treated with recombinant biosynthetic human GH (Norditropin, Novo Nordisk A/S, Denmark) administered sc every evening in a dose of 0.7 U·kg−1·week−1. Blood was drawn before and after three months of treatment, 36 h after the previous GH administration. The studies were approved by the Hospital Ethics Committee of the Beilinson Medical Center and Ministry of Health of Israel, and informed consent was obtained from all parents or adult patients.

Methods

Heparinized blood for plasma GH and insulin determinations, and non-heparinized blood for serum IGF-I and IGFBP-1 measurements, were drawn from all subjects in the morning after an overnight fast. After centrifugation the plasma and sera were stored at −20°C until assayed. For IGFBP-1 determination, serum was deepfrozen, lyophilized and sent to Helsinki for analysis. After reconstitution with appropriate volumes of distilled water, the measurement of serum IGFBP-1 concentrations was carried out by a radioimmunoassay (RIA) essentially as described before (10), but purified IGFBP-1 from human amniotic fluid (11) and polyclonal rabbit anti-IGFBP-1 antiserum were used (12). Iodination was carried out with a lactoperoxidase method (10). Antiserum bound 25–30% of 125I-IGFBP-1 in a final dilution of 1:50,000–1:150,000. Sensitivity of the assay was 2.3 μg/l. This assay measures both IGF-bound and free IGFBP-1 (13). The intra- and interassay coefficients of variation were from 6 to 10%. Serum IGF-I was determined by a disequilibrium RIA using a kit from INCSTAR (Stillwater, MN) (14). Before the assay, serum IGFBPs were removed by reverse-phase chromatography. Serum insulin was measured according to Heding (15) by a double antibody technique with an insulin standard donated by Novo Nordisk A/S, Denmark. Plasma GH was determined with a double antibody modification of the RIA described by Laron and Mannheimer (16), using GH RP-1 standard donated by the National Pituitary Agency (Baltimore).

Statistical analyses were done with analysis of variance, paired or unpaired t-test and with linear regression analysis where appropriate, after logarithmic transformation of the values with uneven distribution. Results are given as mean ± SD.

Result

Baseline hormone and IGFBP-1 concentrations

Growth hormone. As expected, the basal plasma GH level was elevated in the LTD patients. In the children the mean concentration was 0.93 ± 1.53 pmol·l−1 and in the adults 0.45 ± 0.83 pmol·l−1. The children with constitutional growth retardation had fasting plasma growth hormone concentration (0.12 ± 0.07 pmol·l−1) similar to that of the control prepubertal children (0.12 ± 0.02 pmol·l−1).

Insulin. The mean basal serum insulin concentration in children with constitutional short stature and low body mass index was significantly lower than in the other groups (LTD children/adult LTD patients, Table 1). In adult GHD patients the findings varied according to different diagnostic entities: patients with MPHD had a pretreatment serum insulin level similar to that in healthy controls. In patients with IGHD the mean insulin concentration was higher than that in the adult control subjects (Table 1).

IGF-I. Serum IGF-I was undetectable or very low in both LTD children and adults (Table 1), as well as in patients with GHD. In prepubertal constitutionally short children, serum IGF-I concentration was normal for age
Table 1. Pertinent clinical data and IGFBP-1, IGF-I and insulin levels in LTD patients, hGH deficient patients and children with constitutional short stature, compared to healthy controls (mean ± sp).

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Age (Years)</th>
<th>Age (Range)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body mass index (kg/m²)</th>
<th>IGFBP-1 (µg·l⁻¹)</th>
<th>IGF-I (nmol·l⁻¹)</th>
<th>Insulin (pmol·l⁻¹)</th>
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<tbody>
<tr>
<td>LTD patients</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Children</td>
<td>6</td>
<td>8.6 ± 4.8</td>
<td>(1.8–14)</td>
<td>90 ± 20</td>
<td>16.7 ± 9.1</td>
<td>18.8 ± 4.4</td>
<td>368 ± 299.4*</td>
<td>4.1 ± 1.7</td>
<td>64.5 ± 45.2†</td>
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<tr>
<td>Adults</td>
<td>9</td>
<td>31.4 ± 3.8</td>
<td>(25–37)</td>
<td>122 ± 12</td>
<td>40.4 ± 9.3</td>
<td>26.8 ± 2.6</td>
<td>82.4 ± 50.3</td>
<td>7.2 ± 2.9</td>
<td>61.2 ± 37.3††</td>
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<td>hGH deficiency</td>
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<tr>
<td>Children</td>
<td>11</td>
<td>7.6 ± 3.4</td>
<td>(3–13)</td>
<td>95 ± 14</td>
<td>14 ± 6</td>
<td>15.3 ± 0.8</td>
<td>281.6 ± 188.9*</td>
<td>6.6 ± 3.9</td>
<td>58.5 ± 39.0†</td>
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<td>Adults</td>
<td>21</td>
<td>25.9 ± 6.8</td>
<td>(18–36)</td>
<td>157 ± 10</td>
<td>55.7 ± 11.0</td>
<td>22.7 ± 4.5</td>
<td>83.6 ± 59.5</td>
<td>—</td>
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<tr>
<td>MPHD</td>
<td>12</td>
<td>26.8 ± 6.9</td>
<td></td>
<td>162 ± 6</td>
<td>55.5 ± 8.9</td>
<td>21.1 ± 2.8</td>
<td>109.3 ± 57.6**</td>
<td>8.1 ± 4.3</td>
<td>61.3 ± 37.7</td>
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<td>IGHD</td>
<td>9</td>
<td>24.8 ± 6.9</td>
<td></td>
<td>150 ± 9</td>
<td>56.0 ± 14.1</td>
<td>24.9 ± 5.6</td>
<td>55.1 ± 44.9</td>
<td>6.5 ± 3.2</td>
<td>123.4 ± 85.3††</td>
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<td>Constitutional short stature</td>
<td>8</td>
<td>7.0 ± 5.6</td>
<td>(2–11)</td>
<td>108 ± 14</td>
<td>16.3 ± 5.4</td>
<td>13.5 ± 1.5*</td>
<td>258.6 ± 74.9*</td>
<td>18.3 ± 5.4</td>
<td>31.1 ± 11.3</td>
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<td></td>
</tr>
<tr>
<td>Prepubertal</td>
<td>9</td>
<td>4.5 ± 3.0</td>
<td>(1.6–9)</td>
<td>105 ± 15</td>
<td>17.0 ± 4.0</td>
<td>15.3 ± 1.5</td>
<td>67.9 ± 38.2</td>
<td>18.3 ± 1.9</td>
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<tr>
<td>Pubertal</td>
<td>11</td>
<td>13.4 ± 2.1</td>
<td>(10–17)</td>
<td>156 ± 18</td>
<td>45.6 ± 15.0</td>
<td>18.3 ± 3.4</td>
<td>44.7 ± 28.9</td>
<td>38.2 ± 7.1</td>
<td>—</td>
</tr>
<tr>
<td>Adults</td>
<td>20</td>
<td>30.0 ± 4.0</td>
<td>(18–41)</td>
<td>179 ± 3</td>
<td>77.0 ± 2.0</td>
<td>24.0 ± 1.8</td>
<td>57.6 ± 12.0</td>
<td>—</td>
<td>40.2 ± 19.0</td>
</tr>
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</table>

*p < 0.02 vs healthy children; **p < 0.02 vs healthy adults; †p < 0.05 vs children with constitutional short stature; ††p < 0.05 vs health adults.
Fig. 1. Basal IGFBP-1 concentrations in control subjects. Laron type dwarfism, isolated growth hormone deficiency (IGHD), multiple pituitary hormone deficiency (MPHD), and children with constitutional short stature (CSS). Mean ± SD. *p < 0.02 vs healthy adults, **p < 0.02 vs healthy children.

Fig. 2. The response of IGFBP-1 to IGF-I or growth hormone treatment in patients with LTD. growth hormone deficiency, or constitutional short stature. LTD: O = child, ● = adult. GHD: ◻ = child, ■ = adult. ▲ = child.

(Table 1). In pubertal control children the mean concentration of 38.2 ± 7.1 pmol·L⁻¹ was similar to that previously reported for age at puberty (14).

IGFBP-1. The values for each entity of subjects divided by age groups and disease expressions are shown in Fig. 1. In LTD children, the mean serum IGFBP-1 concentra-
tion was 5.4-fold higher; in GHD children it was 4.1-fold higher and in children with constitutional short stature 3.8-fold higher in the prepubertal control group (p < 0.02 vs controls in each group, Fig. 1). In each child with LTD or constitutional short stature, the basal IGFBP-1 value was above the upper normal range with no overlap with the control values. Two LTD children had extremely high values (800, 1070 µg·L⁻¹). In adult LTD patients, the IGFBP-1 concentrations were different from those in the control subjects. In MPHD patients, IGFBP-1 concentration was elevated, whereas in patients with IGHD it was in the normal range (Fig. 1).

Effect of GH or IGF-I therapy

GH. In nine LTD patients (3 children, 6 adults) treated with IGF-I for seven days, serum GH concentrations decreased in all: the average fall was 63% from 1.38 ± 2.07 pmol·L⁻¹ to 0.51 ± 1.11 pmol·L⁻¹ (p < 0.05).

Insulin. In LTD patients, IGF-I therapy did not change serum fasting insulin concentrations in either the children or the adults: the mean value in the whole group remained virtually unchanged (83 ± 54 pmol·L⁻¹ before vs 82 ± 45 pmol·L⁻¹ after therapy). In adult IGHD patients, GH therapy raised serum insulin concentrations by 76% (from 123 ± 85 pmol·L⁻¹ to 218 ± 65 pmol·L⁻¹, p < 0.05), whereas in MPHD patients serum insulin concentrations remained unchanged (62 ± 37 pmol·L⁻¹ vs 65 ± 38 pmol·L⁻¹). In children with constitutional short stature, serum insulin concentration increased during GH therapy by 38% (from 31 ± 11 pmol·L⁻¹ to 43 ± 18 pmol·L⁻¹, p < 0.05). In this group, height increased on the average 3 cm (from 108 ± 14 cm to 111 ± 14 cm) during the three months’ growth.
hormone therapy. However, BMI remained unchanged (13.5 ± 1.6 kg/m²) before and after therapy. Thus, the increase in insulin concentration was not caused by a development of obesity.

**IGF-I.** In LTD patients, 7-day IGF-I therapy did not significantly increase serum IGF-I concentration, as determined 24 h after the previous injection (7.1 ± 3.2 nmol·l⁻¹ before vs 8.5 ± 6.9 nmol·l⁻¹ after therapy). During GH, IGF-I concentration increased in MPHD patients 2.7-fold from 8.7 ± 4.5 nmol·l⁻¹ to 23 ± 8.3 nmol·l⁻¹ (p < 0.02) and in IGHD patients by 2-fold from 11.2 ± 11.2 nmol·l⁻¹ to 22.9 ± 11.4 nmol·l⁻¹ (p < 0.05). In children with constitutional short stature, IGF-I concentration did not change during growth hormone therapy (18.3 ± 5.4 nmol·l⁻¹ before vs 22.4 ± 7.7 nmol·l⁻¹ after therapy).

**IGFBP-1.** In response to IGF-I administration, the IGFBP-1 values decreased by 34% and 44% in two out of the three LTD children who had an increased basal IGFBP-1 concentration. In an infant with very high pre-

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**Fig. 4.** The effect of intravenous administration of IGF-I (75 µg·kg⁻¹) on serum IGF-I, insulin, IGFBP-1 and glucose concentrations in eight patients with Laron type dwarfism. Mean ± SD. *p < 0.05, **p < 0.001 vs 0 min.

**Fig. 5.** The effect of subcutaneous administration of IGF-I 120 or 150 µg·kg⁻¹ on serum IGF-I, insulin, IGFBP-1 and glucose concentrations in nine patients with Laron type dwarfism. Mean ± SD. *p < 0.05, **p < 0.001 vs 0 min.
treatment value, IGFBP-1 remained high after 7 days of IGF-I treatment (Fig. 2). In adult LTD patients with a normal basal IGFBP-1 concentration, the IGFBP-1 level remained unchanged during IGF-I therapy. In children with GHD, GH replacement therapy resulted in a 29% decrease in serum IGFBP-1 concentration, from 205.6 ± 38.0 μg·l⁻¹ to 146.5 ± 25.4 μg·l⁻¹ (p < 0.05). In the adult GHD patients treated with GH, IGFBP-1 concentration decreased by 52% from 99.2 ± 60 μg·l⁻¹ to 47.2 ± 30.8 μg·l⁻¹ (p < 0.05). The fall in serum IGFBP-1 concentration during GH treatment was correlated with the baseline IGFBP-1 concentration (r = 0.86, p < 0.001, Fig. 3). In children with constitutional growth delay, three months’ GH therapy decreased the IGFBP-1 concentration by 17%, from 259 ± 75 μg·l⁻¹ to 216 ± 55 μg·l⁻¹ (p < 0.02) (Fig. 2). There was an inverse correlation between fasting IGFBP-1 and insulin concentrations in GHD patients as determined before and during the growth hormone therapy (r = -0.66, p < 0.0001). A similar inverse relationship was also observed in LTD patients (r = -0.57, p < 0.05), but not in children with short stature.

**Effect of IGF-I injection**

After intravenous injection of IGF-I, serum IGF-I concentration increased in LTD patients 10-fold and remained elevated for the 120 min follow-up period (Fig. 4). The increase in serum IGF-I was associated with a rapid decrease (p < 0.001) in both plasma glucose and serum insulin concentrations and with a slow 40% rise (p < 0.05) in IGFBP-1 concentration. Following subcutaneous injection of 120 or 150 μg·kg⁻¹ IGF-I, there was a 6-fold rise in serum IGFB-I, a 54% fall in serum insulin (p < 0.02), a small decline in serum glucose and a 60% rise in IGFBP-1 (p < 0.02, Fig. 5). Twenty-four hours after the IGF-I injection, serum IGF-I concentrations were slightly higher than the basal values, whereas the serum IGFBP-1 level was similar to the baseline value. The 24 h serum insulin concentration was determined in only two patients. In both, the values (71.3 pmol·l⁻¹ and 18.0 pmol·l⁻¹) were lower than before the injection of IGF-I (162.9 pmol·l⁻¹ and 46.6 pmol·l⁻¹, respectively).

**Discussion**

The current study was designed to investigate the regulation of serum IGFBP-1 concentration in man. In particular, we studied the interrelationship of IGFBP-1 and IGF-I and GH. For this purpose, we examined patients with either IGF-I or GH deficiency. These patients were evaluated in the basal state, after acute IGF-I administration or following a chronic therapy with either IGF-I or GH.

Basal serum IGFBP-1 concentration was elevated in four groups of patients: children with chronic IGF-I deficiency, growth hormone deficiency, or constitutional short stature, and in adults with multiple pituitary hormone deficiency. In all these groups, chronic treatment with IGF-I or with GH decreased the serum IGFBP-1 concentration. Moreover, in adult patients there was a correlation between the pretreatment IGFBP-1 concentration and the decline during GH treatment substitution. Thus, a treatment aiming to normalize IGF-I or GH deficiency hormone deficiency, or both, also decreased elevated IGFBP-1 concentration towards normal.

Several mechanisms may be considered to explain the elevated IGFBP-1 concentrations in these patient groups. First, IGF-I may down-regulate IGFBP-1 secretion. Serum IGF-I concentration was low in children with LTD or GH deficiency, as also reported previously (19). Thus, low IGF-I or GH concentration may have contributed to the elevated IGFBP-1 concentrations. The decrease in IGFBP-1 concentrations after IGF-I or GH treatment in these patients further supports a negative feedback mechanism between IGF-I and IGFBP-1, either direct or indirect.

Secondly, an inverse correlation between insulin and IGFBP-1 levels has been reported in vivo (17, 20, 21) and in vitro (22). Insulin infusion reduces the serum IGFBP-1 concentration in healthy man in a dose-dependent manner (17, 20), and in type 1 diabetic patients with low insulin levels the IGFBP-1 level is elevated (20). Moreover, during physical exercise a fall in plasma insulin is associated with a rise in IGFBP-1 concentration (21). In the current study, chronic GH substitution increased serum insulin concentrations simultaneously with a fall in IGFBP-1 in patients with GHD or constitutional short stature. In addition, we observed an inverse relationship between fasting serum insulin and IGFBP-1 concentrations in Laron dwarfs and GH-deficient patients. After acute intravenous or subcutaneous IGF-I administration, opposite changes were observed in serum insulin and IGFBP-1 concentrations. Although correlations or simultaneous alterations do not prove a causal relationship, these observations support the hypothesis of a regulatory role of insulin on serum IGFBP-1 concentrations.

After acute IGF-I administration, plasma glucose concentrations fell together with insulin, as previously reported (23). Thus, under these conditions either insulin, glucose or both could have contributed the changes in serum IGFBP-1 concentration (24). The fact that the IGFBP-1 levels did not increase as quickly as insulin decreased after IGF-I administration further denotes that the fall in insulin concentration may not be the only element determining the rise in IGFBP-1. Whether the rise in serum IGFBP-1 concentration is due to a fall in glucose and insulin alone, or whether a possible simultaneous rise in counterregulatory hormones (catecholamines, cortisol, glucagon) contributes to this rise is unclear. This question could be solved if IGF-I was given during a maintenance of normoglycemia. Since we did not have a control study without IGF-I injection, we do not know exactly the influence of
diurnal variations, as such, on IGFBP-1 concentrations (25). Since the follow-up time was short (120 min), the effect of diurnal variation is probably very small, however.

Previous studies have demonstrated lower than normal IGFBP-1 concentrations in acromegaly (26), and a fall in IGFBP-1 concentration in infertile women during GH therapy (27). In the current study, IGFBP-1 concentrations were elevated in LTD children and in children or adults with GH deficiency. In GHD patients and in those with constitutional short stature, treatment with GH resulted in a fall in IGFBP-1. The fall in GHD patients was proportional to the pretreatment value. These data, together with previous observations, suggest a relationship between IGFBP-1 and GH concentrations. Whether GH regulates IGFBP-1 directly or via IGF-I or insulin, cannot be determined from the current data. GH was grossly elevated in LTD patients, yet the IGFBP-1 concentration was increased only in the children in contrast to the adults. These data suggest that GH, at least in part, has its effect on IGFBP-1 via IGF-I, and possibly also via insulin.

Taken together, the current data along with previous observations suggest a multifactorial regulation of serum IGFBP-1 concentration. These factors involve at least insulin, GH and IGF-I. With GH or IGF-I replacement therapy, IGFBP-1 concentrations were reduced towards the normal. Recent reports indicate the IGF-I treatment of LTD patients induces a number of anabolic effects (9, 28, 29). The observed changes in IGFBP-1 following IGF-I or GH administration may be linked to these effects.

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