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GH has both diabetogenic and insulin-like actions. Supraphysiological GH doses are known to reduce insulin sensitivity \( S_I \), but lower doses are less well studied. We therefore compared the effects of two physiological GH doses (intermediate, 0.0033 mg/kg/d; low, 0.0017 mg/kg/d) with the standard adult GH deficiency replacement dose (standard, 0.008 mg/kg/d) on \( S_I \), \( \beta \)-cell function, IGF-I, and IGF binding proteins (IGFBPs)-1 and -3 in healthy adults.

Eleven healthy nonobese volunteers (4 males and 7 females, aged 21–38 yr) received 7 daily injections of the standard and intermediate GH doses, and 10 (5 males and 5 females, aged 21–38 yr) received the low dose. Fasting blood samples were collected daily (days 1–8). \( S_I \) and \( \beta \)-cell function were calculated using the Homeostasis model assessment.

All GH doses increased IGF-I and IGFBP-3 levels, with the standard dose inducing the greatest rise \(( P<0.001)\). At day 2 vs. baseline, all three doses increased the IGF-I/IGFBP-3 ratio, but only the standard dose lowered IGFBP-1 levels \(( P=0.03)\). The standard dose reduced \( S_I \) \(( P=0.01)\), whereas the intermediate dose increased \( S_I \) \(( P<0.005)\) and lowered fasting insulin levels \(( P<0.01)\). The low dose did not modify \( S_I \), but reduced fasting glucose levels \(( P<0.0001)\) and increased \( \beta \)-cell function \(( P=0.001)\). Males demonstrated higher IGF-I and IGFBP-3 responsiveness to the standard dose than females. Males also showed greater increase in \( S_I \) and decrease in fasting glucose levels on both intermediate and low doses.

In conclusion, the metabolic effects of GH are dose- and gender-dependent. The standard adult GH deficiency replacement dose induced insulin resistance, whereas lower doses improved \( S_I \), especially in males. The low GH dose lowered fasting glucose levels and could represent the optimal dose to stimulate \( \beta \)-cell function without compromising \( S_I \) in insulin-resistant GH-deficient adults. (J Clin Endocrinol Metab 87: 1989–1995, 2002)

Recent evidence has implicated the role of GH as an important regulator of metabolism (1, 2) and glucose homeostasis (3, 4) in adults. Although several studies have demonstrated that exogenously administered supraphysiological GH doses exert diabetogenic effects (5–7), it has long been known that GH may also induce hypoglycemia, thus mimicking the action of insulin (8–10). Previous studies examining the effects of GH insulin sensitivity \( S_I \) in normal subjects have yielded contrasting results. Some investigators have demonstrated acute insulin-like effects of GH on carbohydrate metabolism (8, 9), whereas others have demonstrated diabetogenic effects at the insulin receptor and postreceptor sites (11, 12).

These contradictory results and conclusions raise the question as to whether GH doses lower than those used in previous studies have distinct, independent effects on \( S_I \) and blood glucose and plasma insulin levels. The present study was therefore undertaken to analyze the early action of physiological to pharmacological doses of GH, administered over 7 d, on fasting glucose and insulin, \( S_I \), IGF-I, IGFBP-1, and IGFBP-3 levels in young healthy adults. Our physiological GH doses (intermediate dose, 0.0033 mg/kg/d; low dose, 0.0017 mg/kg/d) represent the closest approximation to daily physiological GH production rates in adults; these decrease with age (13–15) and are estimated as approximately 47 μg/liter·d (or approximately 0.003 mg/kg·d for an average 70-kg individual) in middle-aged women and approximately 15 μg/liter·d (or approximately 0.0011 mg/kg·d for an average 70-kg individual) in men (16). We compared the effects of these physiological GH doses with the standard GH replacement dose (standard dose, 0.008 mg/kg·d) derived from the reported average GH dose used in the United Kingdom and Europe (17).

Subjects and Methods

Subjects

In total, 14 young healthy nonobese adult volunteers participated in the study. Eleven subjects (4 males and 7 females; age range, 21–38 yr) received two 7-d courses of the standard and intermediate GH doses. After the completion of administration of the 2 GH doses, the same 11 subjects were invited to receive the low GH dose. Three subjects declined...
and were replaced by three other volunteers (one subject subsequently withdrew for unrelated reasons). Thus, 10 subjects (5 males and 5 females; age range, 21–38) successfully completed the low-dose phase of the study. The inclusion criteria were healthy subjects without any previous significant medical history and not taking any regular medication. The study was approved by the local hospital Ethics Committee, and informed consent was obtained from all of the subjects.

**GH administration**

We chose two GH doses that approximated to the estimated daily physiological adult GH production rate (intermediate dose, 0.0033 mg/kg; low dose, 0.0017 mg/kg) and one dose that represented the standard GH replacement dose used in GH-deficient adults (standard dose, 0.008 mg/kg).

Subjects were instructed to self-administer GH by sc injection in the thigh, daily at 2200 h on 7 consecutive days for each dose. A 7-d washout period separated the standard and intermediate dose phases. During these two treatment phases, subjects used a Genotropin pen (Pharmaeutics Ltd., Stockholm, Sweden). This injection device administers preset GH doses adjustable in 0.133 mg (0.4 U) increments (clicks), and therefore the nearest number of clicks. The low dose was administered using a 0.3-ml syringe, thus allowing the individual weight-dependent doses to be administered to the nearest 0.053 mg (i.e., minimal increments of 0.01 ml from the syringe are equivalent to 0.053 mg of GH).

**Blood samples and assays**

During all three treatment phases, a venous blood sample was collected between 0800 and 1000 h after an overnight fast (day 1, or baseline) and on each morning following the evening GH injections (days 2–8). Blood glucose concentration was measured daily, and the remaining sample was spun down and stored at −20°C until assayed for insulin, GH, IGF-I, IGFBP-1, and IGFBP-3 levels.

Blood glucose concentration was measured on whole blood using a YSI, Inc. (Yellow Springs, OH) model 2300 stat plus analyser (Farnborough, Hants, UK). The intra-assay coefficient of variation (CV) was 2.6% at 4.4 mmol/liter, and interassay CV were 8.8 and 3.1% at 4.4 mmol/liter and 14.9 mmol/liter, respectively. Plasma insulin was measured using the Coat-A-Count RIA from Diagnostic Products (Llanberis, Gwynedd, UK) according to the manufacturer’s instructions. Intra-assays CV were 3.5 and 3.2% and interassay CV were 7.2 and 4.9% at 50 and 200 mU/liter, respectively. Serum GH was measured by RIA (Endocrine Sciences, Inc.). Interassay CV was 12% at 19.2 mU/liter, and sensitivity was 0.17 mU/liter. Serum IGF-I, IGFBP-3, and IGFBP-1 concentrations were determined by immunoradiometric assays using commercial kits (DSL, Tooting, London, UK) according to the manufacturer’s instructions. For IGF-I, sensitivity was 0.080 ng/ml, intra-assay CV were 3.4 and 1.5% at 9.4 and 263.6 ng/ml, respectively, and equivalent interassay CV were 8.2 and 3.7%. For IGFBP-3, sensitivity was 0.5 ng/ml; intra-assay CV were 3.9, 3.2, and 1.8% at 7.4, 27.5, and 82.7 ng/ml, respectively; and equivalent interassay CV were 0.6, 0.5, and 1.9%, respectively. For IGFBP-1, sensitivity was 0.33 ng/ml; intra-assay CV were 5.2, 4.6, and 2.7% at 5.2, 50.2, and 144.6 ng/ml, respectively; and equivalent interassay CV were 3.5, 6.0, and 3.6%, respectively.

**Calculations**

The IGF-I/IGFBP-3 molar ratios were calculated by taking into account the molecular weights of IGF-I (7.6 kDa) and IGFBP-3 (50 kDa).

The Homeostasis model assessment (HOMA), previously described by Matthews and co-workers (18, 19), is a structural model of glucose/insulin interaction, with mathematical equations describing the functioning of the major effector organs. Assessment of the fasting glucose and insulin concentrations in each subject allows the evaluation of the combination of β-cell function and Sglu using the HOMA-CIGMA Calculator Program (18). With such a method, high HOMA scores denote high Sglu. The HOMA method has been previously validated against independent measures of Sglu and β-cell function, including clamp-derived measures (20–22).

Percentages of baseline values (day 1 value = 100%) were calculated in each individual for Sglu, β-cell function, and all other hormone values to assess changes from baseline.

**Statistical analyses**

Statistical analyses were performed using SPSS for Windows (version 10.0, SPSS, Inc. Chicago, IL). Data are expressed as means ± se. Paired t tests were used to test differences between baseline and treatment values. Regression coefficients (B) with se values were used to describe the gradient of change in any measured parameter against time (in days). Each treatment phase was analyzed longitudinally using ANOVA; and between-dose effects were examined using analysis of covariance to take into account the longitudinal nature of the data from each treatment phase in each subject, although the differences in subjects between each treatment dose excluded a formal within-subject analysis of GH dose effects. The statistical tests were performed on the raw data, and the results are demonstrated in the illustrations as percentages of baseline values (day 1 value = 100%). Pearson’s correlation coefficient was used to calculate correlations. P values less than or equal to 0.05 defined statistical significance.

**TABLE 1. Characteristics of study subjects at start (day 1) of each 7-d GH dose administration**

<table>
<thead>
<tr>
<th>Actual GH dose administered (range)</th>
<th>Intended GH dose (mg/kg)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low 0.0017</td>
<td>Intermediate 0.0033</td>
<td>Standard 0.008</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>30.6 ± 2.0</td>
<td>29.3 ± 1.7</td>
<td>29.3 ± 1.7</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>50%</td>
<td>63.7%</td>
<td>63.7%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.8 ± 5.2</td>
<td>70.4 ± 3.9</td>
<td>69.8 ± 3.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.6 ± 1.2</td>
<td>24.0 ± 0.7</td>
<td>23.8 ± 0.7</td>
</tr>
<tr>
<td>Waist/hip ratio (cm)</td>
<td>0.79 ± 0.03</td>
<td>0.8 ± 0.03</td>
<td>0.8 ± 0.03</td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>345.1 ± 33.6</td>
<td>234.3 ± 15.6</td>
<td>244.3 ± 18.4</td>
</tr>
<tr>
<td>IGFBP-3 (ng/ml)</td>
<td>3388.9 ± 181.1</td>
<td>4216.7 ± 1017.4</td>
<td>4101.6 ± 205.8</td>
</tr>
<tr>
<td>IGFBP-1 (ng/ml)</td>
<td>0.67 ± 0.06</td>
<td>0.4 ± 0.04</td>
<td>0.4 ± 0.04</td>
</tr>
<tr>
<td>Fasting glucose (mmol/liter)</td>
<td>4.7 ± 0.2</td>
<td>4.5 ± 0.1</td>
<td>4.4 ± 0.1</td>
</tr>
<tr>
<td>Fasting insulin (mU/liter)</td>
<td>8.5 ± 1.5</td>
<td>9.1 ± 1.7</td>
<td>8.8 ± 0.9</td>
</tr>
<tr>
<td>Insulin sensitivity (HOMA-S) (%)</td>
<td>100.8 ± 10.4</td>
<td>101.0 ± 9.9</td>
<td>99.4 ± 10.9</td>
</tr>
<tr>
<td>β-cell function (HOMA-B) (%)</td>
<td>118.9 ± 8.8</td>
<td>134.2 ± 17.3</td>
<td>131.8 ± 6.7</td>
</tr>
</tbody>
</table>

Mean ± SEM, except for sex (%) and number of subjects.

*IGF-I/IGFBP-3 molar ratio.*
Results

Characteristics of study subjects

Table 1 presents the baseline characteristics (day 1) for the three GH dose groups. There were no differences with regard to age, height, weight, body mass index, and waist-to-hip ratio between groups at baseline. No significant changes in body size or body composition were seen during treatment with any of the GH doses.

IGF-I and IGFBP levels

IGF-I levels increased on all three GH doses. The standard dose induced the steepest rise in IGF-I levels (B = 12.5 ± 2.0 ng/ml/d; P < 0.001), whereas the intermediate dose (B = 6.2 ± 1.4 ng/ml/d; P < 0.001) and the low dose (B = 8.8 ± 4.2 ng/ml/d; P = 0.04) induced significant but lesser increases (Fig. 1).

The standard GH dose induced the steepest rise in IGFBP-3 levels (B = 123.6 ± 24.1 ng/ml/d; P < 0.001). IGFBP-3 levels increased to a lesser extent on the intermediate (B = 35.7 ± 18.4 ng/ml/d; P = 0.056) and low (B = 40.2 ± 14.9 ng/ml/d, P = 0.009) doses (Fig. 1). The rise in IGFBP-3 levels (day 8 vs. baseline) was significantly greater on the standard dose than on the intermediate (P = 0.008) or low (P = 0.03) doses.

The IGF-I/IGFBP-3 molar ratio increased by a similar percentage of baseline on all three GH doses (day 2 vs. baseline standard dose, P = 0.004; intermediate dose, P = 0.01; low dose, P = 0.002), and these elevations persisted from day 2 to day 8 (Fig. 1).

A significant reduction in IGFBP-1 was seen on the standard GH dose (day 2 vs. baseline, P < 0.05), and IGFBP-1 levels remained low up to day 8. However the intermediate and low doses did not produce any significant changes in IGFBP-1 levels (day 8 vs. baseline, intermediate dose, P = 0.8; low dose; P = 0.5) (Fig. 1).

Insulin and glucose metabolism

The standard GH dose lowered S_i (day 8 vs. baseline, P = 0.04), with a small increase in fasting insulin levels (day 8 vs. baseline, P = 0.04). However, there were no changes in fasting glucose levels (B = 0.01 ± 0.015 mmol/liter/d; P = 0.4) or β-cell function (B = 1.77 ± 1.31%/d; P = 0.2) (Fig. 2).

Conversely, the intermediate GH dose increased S_i (B = 3.0 ± 1.0%/d; P < 0.005), and reduced fasting insulin levels (B = -0.25 ± 0.1 mU/liter/d; P = 0.009). Again, fasting glucose levels (B = 0.02 ± 0.02 mmol/liter/d; P = 0.3) and β-cell function (B = -1.53 ± 1.25%/d; P = 0.2) were unchanged (Fig. 2).

The low GH dose produced a steady decline in fasting glucose levels (B = 0.08 ± 0.2 mmol/liter; P < 0.0001); com-
pared with baseline, fasting glucose levels were 12% lower on day 8 ($P < 0.03$). This GH dose also produced a rise in $\beta$-cell function ($B = 6.31 \pm 1.82\%$; $P = 0.001$), although fasting insulin levels ($B = 0.07 \pm 0.1 \text{ mU/liter}; P = 0.5$) and $S_I$ ($B = -0.17 \pm 0.89\%$; $P = 0.8$) were unchanged (Fig. 2).

Table 2 shows a summary of the biochemical responses for the three GH doses.

**Between-dose effects**

Analysis of covariance using the whole dataset demonstrated that increasing GH dose was associated with a significant linear reduction in $S_I$ ($B = -112.6 \pm 32.8\%$; $P = 0.0007$) and increase in fasting insulin levels ($B = 10.06 \pm 2.82 \text{ mU/liter}; P < 0.001$). The final percentage change in $S_I$ (day 8 minus day 1) was inversely related to the final percentage change in IGF-I levels ($r = -0.39; P = 0.03$), but not with the changes in IGFBP-3 or IGFBP-1 levels.

**Gender differences**

The IGF-I response to the standard GH dose was higher in males ($B = 21.9 \pm 3.1 \text{ ng/ml-d}; P < 0.001$) than females ($B = 7.3 \pm 2.2 \text{ ng/ml-d}; P = 0.002$), but the intermediate and low doses increased IGF-I levels similarly in both genders. Similarly, males showed a greater IGFBP-3 response to the standard dose ($B = 171.2 \pm 28.1 \text{ ng/ml-d}; P < 0.001$) than females ($B = 96.4 \pm 33.9 \text{ ng/ml-d}; P = 0.006$), but there were no gender differences in the effects of the physiological doses on IGFBP-3 levels.

**TABLE 2. Summary of the biochemical responses for the three GH doses**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low (0.0017)</th>
<th>Intermediate (0.0033)</th>
<th>Standard (0.008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I</td>
<td>$a$</td>
<td>$a$</td>
<td>$a$</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td></td>
<td>$b$</td>
<td>$b$</td>
</tr>
<tr>
<td>IGF-I/IGFBP-3 molar ratio</td>
<td></td>
<td>$c$</td>
<td>$c$</td>
</tr>
<tr>
<td>IGFBP-1</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>$S_I$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>$\beta$-cell function</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
</tbody>
</table>

$\uparrow$, Increase; $-$, unchanged; and $\downarrow$, decrease. $^{a}P < 0.001$, $^{b}P < 0.01$, and $^{c}P < 0.05$.
In males, the physiological GH doses significantly decreased fasting glucose levels (low dose, B = -0.11 ± 0.03 mmol/liter d, P = 0.001; intermediate dose, B = -0.04 ± 0.02 mmol/liter d, P = 0.03) and increased SI (low dose, B = 1.92 ± 0.9%/d, P = 0.04; intermediate dose, B = 4.6 ± 1.6%/d, P = 0.007). In females, the low and the intermediate doses decreased fasting glucose (B = -0.06 ± 0.03 mmol/liter d; P < 0.05) and insulin (B = -0.31 ± 0.14 μU/liter d; P < 0.05) levels, respectively.

**Discussion**

This study addressed the alterations in levels of IGF-I, IGFBP-1, IGFBP-3, and insulin and glucose homeostasis during a 7-d daily administration of recombinant GH in young healthy adults. All three GH doses increased IGF-I and IGFBP-3 levels, and only the standard dose reduced IGFBP-1 levels. Interestingly, GH effects on S_I varied between the doses. Although the standard adult GH deficiency replacement dose lowered S_I, the intermediate GH dose increased S_I with a concomitant reduction in fasting insulin levels, and on the low-dose fasting glucose levels decreased and β-cell function increased.

Circulating IGF-I is mostly bound to IGFBP-3 and acid labile subunit, and this ternary complex has a plasma half-life of approximately 15 h (23). The stimulatory effects of GH on IGF-I and IGFBP-3 levels in healthy adults have been previously demonstrated (24) with two higher GH doses than those used in our study. Our highest GH dose (standard dose, 0.008 mg/kg d) induced the greatest rise in IGF-I and IGFBP-3 levels, whereas our two lower physiological GH doses (intermediate, 0.0033 mg/kg d; and low, 0.0017 mg/kg d) appeared to have similar stimulatory effects on IGF-I and IGFBP-3 levels. Ghigo et al. (25) demonstrated a clear dose-response effect of GH on IGF-I and IGFBP-3 levels; however, in that study the minimum doses that were effective in inducing IGF-I and IGFBP-3 levels were 0.0025 and 0.005 mg/kg d, respectively, which are higher than our low dose (0.0017 mg/kg d). The lack of dose-response effect between our lower GH doses possibly suggests a threshold effect in the induction of IGF-I and IGFBP-3.

No consistent changes were seen with IGFBP-1 levels; only the standard dose induced a significant reduction in IGFBP-1 levels. This observation could be explained by the effects of the standard dose on fasting insulin levels; as this dose increased circulating insulin levels, this induced a reduction in IGFBP-1 levels in a reciprocal manner.

We also analyzed a single fasting GH level on each day during each treatment phase in each subject (data not shown) and found that GH levels were unchanged, even after the administration of the standard GH dose. However, this is not surprising because the timing of blood samples taken for GH analysis was at least 10 h post GH injection.

For the standard GH dose (0.008 mg/kg d), although fasting glucose levels were unchanged, the rise in insulin levels and the corresponding deterioration in S_I indicates that conventional GH replacement doses may have anti-insulin actions per se independent of endogenous GH levels. Indeed, Fowelin et al. (6) demonstrated a temporary reduction in S_I in a group of GH-deficient adults after 6 wk, with partial restoration of pretreatment S_I after 26 wk of GH therapy. However, the GH dose used in that study was almost 3-fold higher than our standard dose, and the partial improvement in S_I may be secondary to increased lean body mass and decreased body fat associated with prolonged GH therapy. In vivo studies have shown that GH administration produces a rapid reduction of forearm muscle uptake of glucose within 10 min (26), and this GH-induced insulin resistance may be due to alterations in insulin receptor function and post-receptor coupling (11).

Previous trials in GH-deficient adults have used GH doses based on body weight or body surface area, adopted from experience in GH-deficient children, and have not taken into account the possibility of individual responsiveness to GH (27). A number of these trials have reported an increased incidence of side effects, particularly in older patients (28). Therefore, there has been a move toward lower GH replacement doses in adults that do not compromise their subjective and objective improvements in sense of well-being and energy (29–31). The use of low GH replacement doses in GH-deficient adults is also advocated to minimize the risk of GH over-replacement, subsequent side effects (29, 32), and the development of insulin resistance (33). GH therapy therefore should be commenced on a low starting dose (34), independent of body weight or body surface area, which mimics normal physiological GH production.

GH-induced insulin resistance has been demonstrated in children treated with daily supraphysiological GH doses using indirect measures of S_I in both short- and long-term studies (35, 36). Paradoxically, Press et al. (37) reported that when GH-deficient children were treated with alternate-day GH therapy, fasting hypoglycemia occurred 36–60 h after each injection. Serum GH levels peaked at 3–6 h after each injection and returned to baseline by 24 h (38), whereas circulating IGF-I levels peaked 19 h post injection, and then fell slowly with a half-life of approximately 20 h (39). Thus, on the second or third day post injection, raised IGF-I levels were not accompanied by elevated GH levels, and the observed fasting hypoglycemia could be due to insulin-like metabolic effects of IGF-I unbalanced by any GH-induced insulin antagonism.

On daily intermediate dose GH administration, we observed an increase in S_I without hypoglycemic episodes, possibly because adults are relatively more insulin resistant than GH-deficient children (35). Low-dose IGF-I therapy has been shown to improve S_I in vitro and in vivo in normal subjects and also in patients with type 1 diabetes (40), and therefore mild improvement IGF-I bioavailability generated by the intermediate dose could explain the improvement in S_I. Adamson et al. (41) demonstrated inhibitory effects of GH on splanchnic glucose production, and this could also explain the improved S_I seen with the intermediate dose.

More surprising was the effect of the low (0.0017 mg/kg d) GH dose on reducing fasting glucose levels and increasing β-cell function, without altering fasting insulin levels. These paradoxical data may reflect the limitations of the HOMA method of assessing β-cell function. A possible explanation is that there may be an increase in insulin-stimulated glucose disposal causing the lowering of fasting glucose levels that were seen; and this sustained insulin release must suggest
alterations in β-cell response to ambient blood glucose concentrations. It is also possible that this dose lowers glucose levels by inhibition of splanchnic glucose production (41), or by direct β-cell stimulation. Direct insulinotropic effects on the β-cell and increased insulin secretion have been demonstrated after GH therapy (1, 2), but the doses used in those studies were relatively high. Indeed, high-dose GH administration in dogs resulted in a large initial rise in insulin secretion but was associated with the early development of insulin resistance (42).

Hwu et al. (43) recently found a small but significant improvement in Sβ after 12 months of GH replacement in GH-deficient adults. The subjects in that study were almost identical in age (mean age, 29.5 yr) and body mass index (mean, 22.8 kg/m²) to our volunteers and were not insulin resistant before the commencement of GH therapy. However, the mean GH dose used (0.011 mg/kg·d) was higher than our standard dose (0.008 mg/kg·d). The metabolic effect of a physiological GH bolus in the postabsorptive state was studied by Moller et al. (44), who demonstrated stimulation of lipolysis after a lag time of 2–3 h. Plasma glucose, serum insulin, and C-peptide levels remained unchanged, with subtle reductions in muscular glucose uptake and oxidation, reflecting substrate competition between glucose and fatty acids. By contrast, prolonged exposure to supraphysiologically high GH levels induces both hepatic and peripheral (muscular) insulin resistance, increased lipid oxidation, compensatory hyperinsulinemia (33), and subsequent β-cell exhaustion (2). Thus, from the work by Hwu et al. (43), Rosenfalk et al. (33), and Moller et al. (44), GH dose, timing and duration of GH administration, age, baseline body composition, and baseline Sβ all appear to be important factors in determining the metabolic manifestations after GH replacement therapy.

Our study also confirmed gender differences in the stimulatory effects between GH doses on fasting glucose and insulin levels, Sβ, IGF-I, and IGFBP-3 levels. Indeed, Ho et al. (13) previously reported that both spontaneous and stimulated GH levels are higher in females, and Ghigo et al. (25) and Dall et al. (45) demonstrated gender differences in GH-stimulated IGF-I response to low and supraphysiologic doses. The reasons for this discrepancy are unclear, and a possible confounding factor may be due to the interactions between female sex steroids and GH action in the peripheral tissues (46). Another possibility is the effect of androgens in enhancing GH action, as demonstrated by Erfurth et al. (47), and in this case one can speculate that the inhibitory influence of estrogen on GH action in females might be partly due to its indirect, testosterone-lowering effect. These observations in our normal adult cohort support the idea that hypopituitary female patients require higher maintenance GH doses than males for a given biochemical response (48, 49).

In conclusion, this study underlines the role of gender and the differences in the effects of physiologic vs. standard GH replacement doses. Although supraphysiologic doses in GH-deficient adults predispose normal adults to insulin resistance, short-term intermediate dose GH (0.0033 mg/kg·d) therapy unexpectedly improved Sβ, possibly due to increased IGFBP-3 bioavailability, direct splanchnic glucose inhibition, and/or peripheral insulin sensitization. The low (0.0017 mg/kg·d) dose reduced glucose levels and increased in β-cell function, and could therefore be the optimal dose in stimulating β-cell function without necessarily compromising Sβ. The study was conducted over 7 d, and it remains to be seen whether longer-term intermediate (0.0033 mg/kg·d) and low (0.0017 mg/kg·d) GH dose administration is able to sustain the benefits on insulin action and β-cell function and promote as well favorable changes in body composition, lipid parameters, and bone density. Also, whether these beneficial metabolic effects can be extrapolated to pathophysiological conditions associated with insulin resistance, such as obesity, adult GH deficiency, and type 2 diabetes mellitus, merits further study.

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