Gender Difference in the Response of Growth Hormone (GH)-Deficient Adults to GH Therapy

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While individual hypopituitary patients undoubtedly benefit from growth hormone (GH) therapy, there is considerable variability in the response to treatment. Given the expense, possible lack of benefit, and potential risks associated with long-term therapy, we sought to identify characteristics potentially associated with a favorable response to GH replacement. Twelve GH-deficient adults (seven men and five women aged 35.4 ± 2.5 years, mean ± SEM) participated in a 12-month open study of GH replacement (0.125 IU/kg/wk for 4 weeks and 0.25 IU/kg/wk thereafter) designed to examine the impact of GH on body composition, lipid profile, and psychological well-being. Using bioelectrical impedance analysis (BIA), there was a reduction in body fat (BF) and an increase in lean body mass (LBM) and total body water (TBW) ($P < .05$) following 12 months of GH treatment. In addition, there was a significant improvement in psychological well-being as indicated by a decrease in the Nottingham Health Profile (NHP) score ($P < .05$) and a decrease in both total cholesterol ($P = .005$) and low-density lipoprotein (LDL) cholesterol ($P < .03$). GH therapy was associated with an increase in fasting plasma glucose ($P = .008$) and hemoglobin A_{1c} (HbA_{1c} ($P = .06$). When analyzed by gender, the beneficial effect of GH was greater in men versus women for the increment in insulin-like growth factor-1 ([IGF-1] 375 ± 59 *v* 148 ± 73 μg/L, mean ± SEM), increase in LBM (6.8 ± 2.5 *v* −0.06 ± 1.6 kg), reduction in BF (5.6 ± 1.6 *v* 1.0 ± 1.9 kg), and increase in TBW (5.0 ± 1.6 *v* 0.14 ± 1.29 L) ($P < .05$). HbA_{1c} increased significantly in women ($P < .05$). The beneficial effect of GH tended to be greatest in those with the most significant abnormality in baseline values ($P < .05$). The duration of hypopituitarism showed an indirect correlation with the change in total cholesterol ($P < .005$). Baseline IGF-1 levels correlated directly with changes in TBW ($P < .05$). These data indicate that men with GH deficiency appear more responsive to GH therapy than women with respect to the increase in IGF-1 levels and improvement in body composition. In general, patients with the most significant abnormality in baseline values, the highest IGF-1 levels, and the shortest duration of hypopituitarism respond best. With long-term GH therapy, careful monitoring of glucose tolerance is indicated.

FOLLOWING THE DEVELOPMENT of recombinant human growth hormone (GH) in the mid-1980s and the recognition that adult GH deficiency may be associated with a distinct clinical syndrome, numerous investigators have sought to define the role of GH replacement in GH-deficient adults. While randomized clinical trials have repeatedly demonstrated a favorable effect of GH therapy on body composition,[1-6] changes in psychological well-being have been less consistent, with most[7-10] but not all[3,11] studies indicating an improvement. GH effects on serum lipids have also been variable, with studies showing a decrease[1,12,13] or no change[3,14,15] in total cholesterol and an increase[13-16] or no change[12] in lipoprotein(a).

To date, the question of whether GH should be standard replacement therapy for adult hypopituitary patients has not been resolved. While some patients undoubtedly derive benefit from GH therapy, there appears to be considerable individual variation in the response to treatment.[17] In the current climate of fiscal restraint, this variability in response together with the high cost of GH therapy, raise doubt as to whether the widespread prescription of GH would be a cost-effective measure. In addition, long-term data on the safety of GH in terms of the possible mitogenicity, the potential risk of promoting pituitary tumor recurrence, and the consequences of increasing hemoglobin A_{1c} (HbA_{1c})[14] and insulin levels[1,16,18-20] are still lacking.

Given the expense, possible lack of benefit, and potential risks associated with GH treatment, we sought to determine whether baseline clinical characteristics could aid the clinician in identifying individuals likely to derive the most benefit from GH replacement.

SUBJECTS AND METHODS

Patient Characteristics

Twelve hypopituitary patients participated in the study (Table 1). The diagnosis of GH deficiency was based on a peak GH response less than 10 mIU/L following insulin-induced hypoglycemia (n = 10) or L-Dopa (n = 2). All but three patients acquired GH deficiency in adult life. One participant had isolated GH deficiency; the remainder were receiving appropriate pituitary hormone replacement therapy, which was stable for at least 6 months before entry into the study. Five of seven GH-deficient men were receiving intramuscular testosterone replacement for concomitant hypogonadism for 8.2 ± 1.7 years (mean ± SEM) before enrollment in the study. All had normal testosterone levels measured midway between injections prior to commencing GH. All five female GH-deficient subjects were receiving an oral estrogen preparation for hypogonadism for at least 6 months prior to starting GH. Although the study was not placebo-controlled, none of the patients had any other medical intervention or life-style modification during the GH treatment study period.

Study Protocol

This was an open study of GH replacement therapy for 12 months. GH (Genotropin; Pharmacia, Dublin, Ireland) was administered as a single daily subcutaneous injection at a dose of 0.125 IU/kg/wk for the first month and 0.25 IU/kg/wk thereafter. The study was approved by the Ethics Committee of St. Vincent's Hospital, and all patients provided written informed consent.

Physical examination was performed at 3-month intervals, in addition to an assessment of body composition and psychological well-being. Body composition was determined by bioelectrical impedance

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Table 1. Baseline Characteristics of 12 GH-Deficient Patients Studied

Characteristic	Total Group	Males	Females
No. of subjects	12	7	5
Age (yr)	35.4 ± 2.5	33.4 ± 3.1	38.2 ± 4.2
Body mass index (kg/m²)	27.6 ± 1.6	30.2 ± 1.7	23.9 ± 2.3*
Duration of hypopituitarism (yr)	11.0 ± 2.6	7.6 ± 1.2	15.8 ± 5.7
Original diagnosis (n)			
Craniopharyngioma	3	1	2
Pituitary adenoma/apoplexy	3/1	1/1	2/0
Idiopathic	1	0	1
Other (dysgerminoma, meningitis, trauma)	4	4	0
Peak GH response (mIU/L)	2.2 ± 0.6	2.5 ± 1.0	1.7 ± 0.3
Serum IGF-1 (μg/L)	117 ± 35	163 ± 54	51 ± 10*
Hormone replacement (n)			
Thyroxine	10	7	3
Corticosteroids	8	5	3
Sex steroids	10	5	5
Desmopressin	6	4	2

NOTE. Results are the mean ± SEM.
*Significant gender difference, $P < .05$.

analysis (BIA) using a portable impedance analyzer (RJL Systems, Detroit, MI). A two-compartment model was used to calculate total body water (TBW), lean body mass (LBM), and fat mass using equations provided by the manufacturer.[21] Recent data suggest that the change in extracellular water with GH treatment is underestimated by BIA,[22] but other studies have shown a good correlation between changes in body composition measured by the four-compartment model and BIA.[8] Thus, while the absolute changes in body composition recorded by BIA may not be entirely accurate, it is at minimum a useful method for recording qualitative intraindividual changes in body composition.

Perceived health status was evaluated using the Nottingham Health Profile (NHP).[23] The NHP contains 38 items assessing energy, emotional reaction, sleep, social isolation, pain, and physical mobility. Each item was weighted and a score (0 to 100) was then calculated for each dimension independently, with a high score indicative of a high degree of impairment. Fasting blood samples were drawn at 6-month intervals for measurement of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and HbA_{1c}.

Assays

GH levels were measured using a two-site immunoradiometric assay (Medgenix Diagnostics, Fleurus, Belgium). Total cholesterol, HDL cholesterol, triglyceride, and glucose levels were measured in serum by routine methods using a Beckman (Fullerton, CA) Synchron CX7 analyzer. LDL cholesterol was calculated using the Friedwald formula.[24] HbA_{1c} was assayed by high-performance liquid chromatography using the Biomen (Berkshire, UK) Hi-Auto HbA_{1c} instrument with a reference range of 2.0% to 4.9%. Total insulin-like growth factor-1-(IGF-1) levels were measured by an immunoradiometric assay after formic acid–ethanol extraction. The age-adjusted reference ranges were 100 to 350 μg/L (20 to 40 years) and 80 to 300 μg/L (41 to 60 years).

Statistical Analysis

All descriptive statistical results are presented as the mean ± SEM. Differences between the baseline and following 12 months of GH therapy were analyzed using the Wilcoxon signed-rank test. Pearson's product-moment correlation coefficient was calculated to evaluate the relationship between two variables. If more than one baseline variable achieved significance, these variables were tested simultaneously using multiple regression analysis. A P level less than .05 was considered statistically significant.

RESULTS

Serum IGF-1

Following treatment with GH, there was a significant increase in IGF-1 levels from 117 ± 35 μg/L at baseline to 397 ± 67 μg/L at 12 months ($P < .005$). When analyzed according to gender, IGF-1 levels were significantly higher in males versus females both before therapy (163 ± 54 *v* 51 ± 10 μg/L, $P < .05$) and after 12 months of GH therapy (538 ± 57 *v* 199 ± 74 μg/L, $P < .05$). The magnitude of the IGF-1 increase in response to equivalent weight-adjusted GH doses was also greater in males versus females (375 ± 59 *v* 148 ± 73 μg/L, $P < .05$) (Fig 1).

Body Weight

There was no significant change in body weight either in the total group (78.6 ± 6.4 *v* 78.9 ± 6.6 kg) or when males and females were analyzed separately (90.8 ± 6.8 *v* 91.6 ± 7.3 and 62.2 ± 7.5 *v* 61.1 ± 7.0 kg, respectively).

LBM

Overall LBM increased 3.9 ± 1.8 kg ($P < .05$) following 12 months of GH therapy (Fig 2). However, this effect was entirely due to a beneficial impact in men, in whom LBM increased from 70.6 ± 4.4 to 77.4 ± 5.4 kg ($P < .05$), whereas in women it remained essentially unchanged (43.5 ± 4.7 *v* 43.4 ± 4.3 kg, pre-GH *v* post-GH). In the total group, the increase in LBM correlated directly with the baseline IGF-1 level ($r = .67$, $P < .02$) and the peak GH response to stimulation ($r = .64$, $P < .03$). However, when included in a multiple regression analysis using the change in LBM as the dependent variable, neither of these parameters remained statistically significant (Table 2).

Body Fat

Following GH therapy, there was a reduction in body fat (BF), which was significant both for the group as a whole

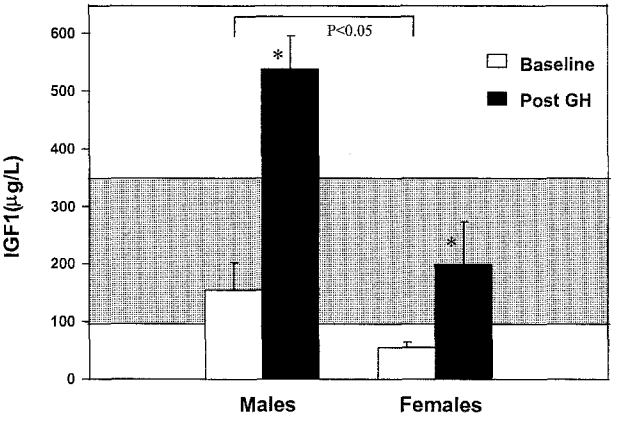

Fig 1. Comparison of IGF-1 levels in GH-deficient males (n = 7) and females (n = 5) before and after 12 months of GH therapy. *Significantly different *v* baseline, $P < .05$. The shaded area represents the age-adjusted reference range for our study population.

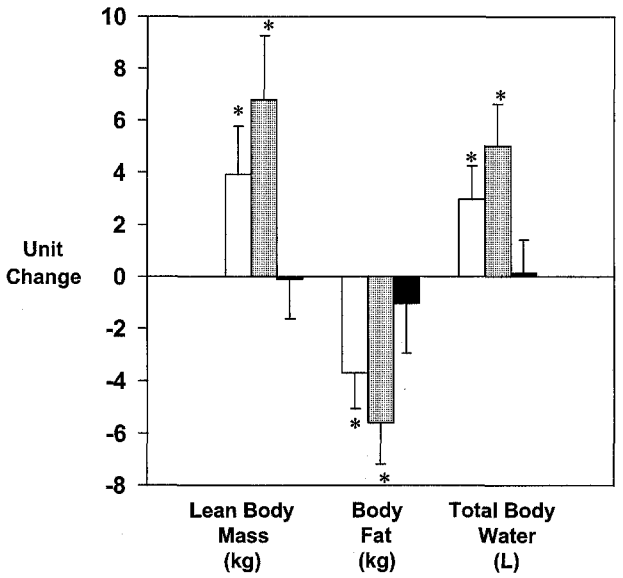

Fig 2. Changes in body composition following 12 months of GH therapy in the total group (□, n = 12), men (▦, n = 7), and women (■, n = 5). *Significantly different *v* baseline, $P < .05$.

(3.7 ± 1.4 kg, $P < .05$) and for males (5.6 ± 1.6 kg, $P < .05$), but not for females (1.0 ± 1.9 kg) (Fig 2). The change in BF correlated inversely with baseline BF ($r = -.59$, $P < .03$) and directly with the duration of hypopituitarism ($r = .63$, $P < .05$), although neither remained statistically significant using multiple regression analysis.

TBW

In the group as a whole and in males, there was a significant increase in TBW, 3.0 ± 1.3 L ($P < .05$) and 5.0 ± 1.6 L ($P < .05$), respectively. No significant change in TBW was observed in females (Fig 2). The increase in TBW correlated directly with baseline IGF-1 levels ($r = .60$, $P < .05$).

NHP

Two patients had a NHP score of 0 at baseline, leaving no room for improvement, and were therefore excluded from analysis. In the remaining patients, the mean weighted NHP score decreased from 119.7 ± 32.6 at baseline to 49.8 ± 23.9 after GH therapy ($P < .05$). The improvement in the NHP score did not achieve statistical significance when either sex was analyzed separately: 92.2 ± 44.4 versus 23.1 ± 11.5 for males ($P < .07$) and 160.9 ± 45.8 versus 89.3 ± 55.8 ($P = .3$) for females. The improvement in psychological well-being was greatest in those with the highest baseline NHP score, where the greatest opportunity for improvement existed ($r = -.75$, $P < .02$). When the different dimensions of the NHP were analyzed independently, a significant improvement was noted for emotions and for energy ($P < .05$).

Lipid Profile

Following GH therapy, there was a significant reduction in total cholesterol in the group as a whole (0.79 ± 0.17 mmol/L, $P = .005$) and in males (0.79 ± 0.09 mmol/L, $P < .02$), but not in females. The reduction in total cholesterol was greatest in those with the highest baseline values ($r = -.65$, $P < .03$) and the shortest duration of hypopituitarism ($r = .81$, $P < .005$). When included in a multiple regression analysis, only the duration of hypopituitarism remained statistically significant. For LDL cholesterol, the reduction following GH therapy was significant in the group as a whole (0.62 ± 0.2 mmol/L, $P < .03$), but it was not significant when males (0.64 ± 0.18 mmol/L) and females (0.6 ± 0.33 mmol/L) were analyzed separately. No significant change was observed in HDL levels in the total group, males, or females. There was a tendency for triglyceride levels to decrease during treatment with GH in the total group (0.45 ± 0.23 mmol/L, $P = .08$) and in males (0.68 ± 0.3 mmol/L, $P = .07$), although statistical significance was not achieved (Table 3).

Glucose and HbA_{1c}

Following 12 months of GH therapy, there was an increase of 0.4 ± 0.1 mmol/L in the mean fasting plasma glucose level ($P = .008$; Table 3). This increase was significant in males (4.5 ± 0.2 *v* 5.1 ± 0.2 mmol/L, $P < .05$) but not in females (4.4 ± 0.1 *v* 4.6 ± 0.1 mmol/L, $P = .14$). In conjunction with the changes in plasma glucose, there was a trend for HbA_{1c} to increase (3.1% ± 0.2% *v* 3.7% ± 0.3%, $P = .06$). The elevation in HbA_{1c} was significant in females (2.8% ± 0.2% *v* 3.7% ± 0.4%, $P < .05$) but not in males (3.3% ± 0.2% *v* 3.8% ± 0.4%, P = NS). The increase in plasma levels of both glucose and HbA_{1c} tended to be greatest in patients with the lowest baseline values ($r = -.56$, $P = .06$ and $r = -.57$, $P < .02$, respectively).

Side Effects

During GH therapy, three patients (all male) complained of edema and arthralgia. This resolved spontaneously in one

Table 2. Pearson's Product-Moment Correlation Coefficients (*r*) for Changes After 12 Months GH Therapy

Parameter	Baseline Value	Baseline IGF-1	Increase in IGF-1	Age	BMI	Duration of GH Deficiency	Peak GH Response to Stimulation
Increase in LBM	.45	.67†	.18	.07	.44	−.33	.64*
Decrease in BF	−.59*	−.40	−.32	−.17	−.54	.63*	−.32
Increase in TBW	.38	.60*	.24	−.01	.42	−.41	.52
Decrease in NHP score	−.75†	.13	−.14	.24	−.10	.5	.32
Decrease in cholesterol	−.65*	−.14	−.34	−.001	−.48	.81†	.04
Increase in plasma glucose	−.56	−.35	.49	−.35	.25	.15	−.28
Increase in HbA_{1c}	−.57*	.19	−.23	.17	−.26	.15	.29

*$P < .05$.
†$P < .02$.

Table 3. Impact of 12 Months of GH Therapy on Serum Lipids, Glucose, and HbA_{1c} in 12 Adults With GH Deficiency

Parameter	Men (n = 7)		Women (n = 5)		Reference Range
	Baseline	Post-GH	Baseline	Post-GH	
Total cholesterol (mmol/L)	6.4 ± 0.3	5.4 ± 0.3†	7.3 ± 1.5	6.5 ± 1.1	3.1-5.8
LDL cholesterol (mmol/L)	3.8 ± 0.1	3.2 ± 0.2	5.2 ± 1.0	4.6 ± 0.7	1.6-4.8
HDL cholesterol (mmol/L)	0.9 ± 0.1	0.8 ± 0.1	1.2 ± 0.2	1.3 ± 0.1	0.6-1.6
Triglycerides (mmol/L)	2.6 ± 0.3	1.9 ± 0.2	1.7 ± 0.4	1.5 ± 0.3	0.1-1.7
Glucose (mmol/L)	4.5 ± 0.2	5.1 ± 0.2*	4.4 ± 0.1	4.6 ± 0.1	3.0-5.9
HbA_{1c} (%)	3.3 ± 0.2	3.8 ± 0.4	2.8 ± 0.2	3.7 ± 0.3*	2.0-4.9

*$P < .05$, †$P < .02$ *v* baseline.

patient and necessitated a 25% reduction in the GH dose in the remainder. There were no significant changes in blood pressure, heart rate, or serum electrolytes. A comparison of the renin-angiotensin-aldosterone axis in patients who did and did not develop edema has been reported previously.[25]

DISCUSSION

To date, there are no absolute indications for prescribing GH therapy in hypopituitary adults, with the decision to use GH replacement being largely an empirical one. While relatively short-term studies have clearly demonstrated a favorable impact of GH on body composition and psychological well-being in some patients,[1-10] there are no data indicating that GH affords a long-term benefit to patients, either by reducing cardiovascular mortality or by decreasing hip fracture as a result of a sustained increase in bone mineral density.[26]

In keeping with previous reports, this study confirms a beneficial impact of GH on body composition, with a 7% increase in LBM and a 20% decrease in BF. In addition, GH treatment was associated with a 14% decrease in total cholesterol, a 13% reduction in LDL cholesterol, and a significant improvement in psychological well-being. However, of particular interest in this study is the demonstration that the beneficial effects of GH are more pronounced in men than in women. This gender difference in the magnitude of the response to GH was consistent across a number of parameters including the increment in IGF-1, increase in LBM, increase in TBW, and reduction in BF. Despite the extensive body of literature now accrued on adult GH replacement therapy and the awareness of the important sex differences in GH secretion in the human,[27] the role of gender has largely been ignored when evaluating the outcome of GH therapy. The first suggestion of a gender difference in the response to GH arose with the publication of two studies in which the GH-induced increment in IGF-1 was significantly lower in GH-deficient women versus men.[17,28] Similar data were obtained in healthy non–GH-deficient subjects, in whom peak IGF-1 levels after a single GH injection were higher in men versus women.[29] Subsequently, Burman et al[30] reported a divergence in the response of GH-deficient males and females to GH therapy across a wide range of parameters, with males experiencing a significantly greater increase in IGF-1 and in markers of bone formation, as well as a significantly greater reduction in BF, total cholesterol, and LDL cholesterol. Most recently, a large Australian multicenter trial of GH therapy reported a greater increment in fat-free mass in GH-deficient males versus females.[6] The present study expands the emerging observations that GH-deficient men demonstrate a significantly greater response to GH treatment than GH-deficient women.

This gender difference in the response to GH is likely mediated by sex steroids, although the exact mechanism is not entirely clear. In both the present study and the study by Burman et al,[30] the severity of GH deficiency as evidenced by the peak GH response to stimulation was similar in men and women. It is possible that concomitant estrogen administration may have played a role in the differential response to GH. Several studies have demonstrated that estrogen has important effects on the GH/IGF-1 axis, causing a decrease in plasma IGF-1 and an increase in IGFBP-1 despite enhancing basal and GH-releasing hormone–stimulated GH secretion.[31-33] Initially, it was thought that the route of estrogen administration was critical in mediating its effects on IGF-1, with oral therapy resulting in higher estrogen concentrations in the liver and consequently a greater impact on hepatic protein synthesis than transdermal preparations.[34,35] However, more recent data suggest that transdermal estrogen has a suppressive effect on IGF-1 levels similar to that of oral preparations when given in doses that result in similar serum estradiol levels.[36] Therefore, it now appears that portal delivery of estradiol is not required to inhibit hepatic IGF-1 synthesis. Given that in the present study and the study by Johannsson et al[17] 100% and 92%, respectively, of the female patients were receiving estrogen replacement therapy, this may well have played a role in the lower IGF-1 levels and the poorer response to GH observed in females. Evidence in support of the estrogen theory is provided by the observation that concomitant estrogen administration attenuated the beneficial effects of GH on body composition and metabolic indices in a cohort of healthy elderly women.[37] On the other hand, in the study by Burman et al,[30] there was no difference in IGF-1 levels or parameters of body composition in response to GH between women who did (n = 8) and did not (n = 7) receive estrogen. Given that there is no conclusive evidence that the beneficial effects of GH are entirely mediated by circulating IGF-1, the importance of estrogen's effect on the IGF-1 axis in mediating the response to exogenous GH administration remains speculative. Further larger studies will be required to resolve this issue. In addition, since the individual GH doses administered in this study were based entirely on body weight without taking into account that GH levels are normally twofold higher in women versus men,[27] it is possible that the gender difference in the response may be entirely attributed to relative underdosing in women. Indeed, it has recently been reported that the dose of GH required to normalize IGF-1 is twice as high in females as in males (1.2 *v* 0.6 IU/d).[28]

While GH therapy clearly had a beneficial impact particularly in men, 25% of patients developed symptoms related to fluid retention requiring a dose reduction. In addition, there was a significant increase in mean plasma glucose levels in the total group and HbA_{1c} in females. The mean HbA_{1c} level remained within the normal range except in two individuals. Despite the abundance of the GH literature, the impact of GH on carbohydrate metabolism has been addressed in relatively few studies. While only one previous study has reported a sustained increase in blood glucose,[1] a progressive increase in HbA_{1c} was observed in a 3-year study of GH replacement therapy, with mean levels exceeding the normal range after 2 years of treatment.[14] There have also been reports of non–insulin-dependent diabetes precipitated by GH therapy.[10,14,17] However, unlike glucose, an increase in insulin has been consistently reported across studies.[1,16,18-20] While GH deficiency is known to be an insulin-resistant state,[16,38-40] GH replacement is paradoxically associated with no change[41] or with worsening[16,19] of insulin sensitivity. Using the hyperinsulinemic-euglycemic clamp technique to determine the effect of 6 months' GH replacement therapy on insulin sensitivity and glucose metabolism, an increase in both glucose and insulin levels was demonstrated at 6 weeks, but was no longer apparent at 26 weeks.[41] The return of insulin sensitivity to baseline with ongoing GH replacement therapy suggests that the favorable changes induced in body composition may counteract the known insulin-antagonistic effects of GH. This hypothesis is supported by the greater increase in HbA_{1c} observed in female subjects in the present study who did not experience favorable changes in body composition. However, a more recent study of 24 months of GH replacement demonstrated a worsening of hyperinsulinemia and defects in insulin action despite significant improvements in body composition.[19] Therefore, it appears that maintenance of normal glucose tolerance in GH-treated GH-deficient adults is likely to depend on the β-cell reserve of the individual and potentially the degree to which body composition is favorably altered.

Based on this study of a small number of patients, it appears that GH-deficient men are more likely to demonstrate a favorable response to GH replacement than GH-deficient women. In general, the patients likely to obtain the most benefit are those with the most significant abnormality in baseline values, the shortest duration of hypopituitarism, and the highest baseline IGF-1 values. Individual titration of the GH dose, with higher GH doses recommended for women independently of body weight, is worthy of further evaluation.

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