

# Gender Difference in Insulin-Like Growth Factor I Response to Growth Hormone (GH) Treatment in GH-Deficient Adults: Role of Sex Hormone Replacement

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## ABSTRACT

GH production in healthy women is about thrice that in men. Yet insulin-like growth factor I (IGF-I) levels are similar, suggesting a lower responsivity to GH in women. In untreated GH-deficient adults, basal IGF-I levels are reportedly lower in females than in males, and the therapeutic recombinant human GH (rhGH) dose required to achieve optimal IGF-I levels is higher in the former, suggesting a pivotal role of estrogens on rhGH requirement in GH-deficient patients. We, therefore, analyzed our 2-yr data on the effect of rhGH on serum IGF-I in 77 GH-deficient patients (33 men, mean  $\pm$  SD age, 37.2  $\pm$  13.8 yr; 44 women, mean  $\pm$  SD age, 36.9  $\pm$  11.9 yr) with due attention to gender differences and to the effects of sex hormone replacement. Of the 44 women, 33 had estrogen substitution. Of the 33 men, 23 were on androgen replacement. Patients (11 premenopausal women and 10 men) not on hormonal replacement were eugonadal.

Basal IGF-I levels in untreated GH-deficient women were significantly lower than in men (8.8  $\pm$  0.7 nmol/L vs. 12.2  $\pm$  0.9 nmol/L;  $P < 0.01$ ), despite similar basal GH levels. The daily rhGH dose per kg body weight required to normalize IGF-I in women was higher than in men, the difference being statistically significant at all time points ( $P < 0.05$ – $0.01$ ). The IGF-I increase ( $\Delta$ ) per IU GH/day/kg over the 24-month period was about twice higher in men than in women. Also calculated on a weight basis, rhGH responsivity (rhGH responsivity =

( $\Delta$ IGF1(nmol/L)/dose (IU/day/kg)) was higher in men than in women at all time intervals ( $P < 0.05$ – $0.01$ ).

Estrogen replacement in women significantly increased rhGH requirement. The rhGH dose per kg body weight required in estrogen-substituted women was significantly higher than in nonestrogen-substituted women ( $P < 0.01$  at  $t = 18$  and 24 months, respectively). In women on estrogen substitution, rhGH responsivity plateaued from 6 months on, whereas in eugonadal women without estrogen substitution the responsivity for rhGH increased over time. In men, the reverse was true; rhGH responsivity increased over time in men on androgen substitution, but plateaued in men without androgen substitution.

The mechanisms underlying this gender difference are not known. Differential influences of estrogens and androgens on the expression of the GH receptor gene and IGF-I messenger RNA may be operative.

The present study confirms short-term data published in the literature on a sex difference in rhGH dose requirement in GH-deficient patients. It further extends the data by demonstrating that this sex difference in GH responsivity persists and changes during the 24 months of the study. Moreover, it shows that estrogen replacement blunts the IGF-I response to rhGH in women, whereas in men with androgen substitution the responsivity increases over time, thus bearing a risk of undertreatment in women and overtreatment in men. (*J Clin Endocrinol Metab* 85: 1121–1125, 2000)

**D**URING CHILDHOOD, secretion of GH shows no difference between boys and girls (1). However, at pubertal age differences can be found between both sexes, integrated GH concentrations in young menstruating women being higher than in young men (2). At the adult age there is still a marked difference between both genders. Most studies show that GH secretion is higher in women than in men, both under basal conditions (3, 4) and after stimulation (5, 6). van den Berg *et al.* (4) reported that the mean daily GH production was thrice greater in women than in men, largely due to an amplitude-specific divergence in the pulsatile mode of GH secretion. This gender difference is closely related to estrogen secretion and possibly influenced by serum

testosterone, as well (7). Indirect evidence for estrogen influence on GH secretion also can be derived from the fact that during the late follicular phase of the menstrual cycle integrated GH concentrations are higher than during the early follicular phase and luteal phase (8). Furthermore, oral estrogen administration has been shown to increase integrated GH concentration both in healthy pre- and postmenopausal women by virtue of a lesser negative feedback due to lowered serum insulin-like growth factor I (IGF-I) concentration (9).

Despite higher GH levels in healthy adult women compared with healthy adult men, no gender difference in basal serum IGF-I concentrations has been demonstrated (10, 11). Remarkably, however, where estrogen administration lowers IGF-I concentrations in healthy women, in men a direct positive correlation between serum testosterone and IGF-I levels has been reported (12), compatible with a gender difference in IGF-I control caused by sex steroids.

In contrast to healthy men and women, IGF-I levels in GH-deficient adults are lower in women than in men (13–15).

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Furthermore, Burman *et al.* (13) and Drake *et al.* (15), in rather short studies (9 and 3 months, respectively), observed a gender difference in recombinant human GH (rhGH) requirement, women needing higher rhGH doses and longer time than men to achieve the same clinical effects and IGF-I levels. Unexpectedly, however, in the GH-deficient women no statistically significant effect of estrogen substitution on IGF-I to rhGH responsiveness was found (13, 15). This may be due partly to the small number of women studied, the rather short treatment period, or to the substitution method used (13, 15). In the rhGH-deficient men the effect of androgen substitution on rhGH requirement was not evaluated at all. This knowledge prompted us to: 1) analyze our data on serum IGF-I-titrated rhGH treatment in a large cohort of 77 GH-deficient adults not only to confirm the presence of a gender difference in rhGH requirement after short-lasting GH replacement, but also to assess its persistence after more prolonged rhGH treatment; and 2) extend literature data on this gender difference by evaluating the effect of sex hormone substitution on IGF-I responsiveness to rhGH in women and also in men.

## Subjects and Methods

### Patients

Seventy-seven patients (33 men, age  $37.2 \pm 13.8$  yr (mean  $\pm$  SD); 44 women, age  $36.9 \pm 11.9$  yr) suffering from GH deficiency, were included in this analysis. GH deficiency was diagnosed when an arginine test revealed a peak GH concentration below 10 mU/L (16). Thirty-three women and 23 men received sex hormonal substitution therapy. Three of the women, all over 50 yr of age, received transdermal estrogen replacement, and the remaining 30 had oral estrogen substitution. Most men received parental androgen substitution ( $n = 19$ ), whereas only four had oral replacement therapy. None of the men had transdermal substitution. Twenty-one patients (11 premenopausal women and 10 men) were eugonadal.

Due to pituitary pathology, most patients had multiple pituitary deficiencies and additionally received adequate hormonal replacement therapy. Pituitary pathology was idiopathic (multiple or isolated) in 19 patients and was caused by pituitary adenoma in 23 patients; craniopharyngioma in 13 patients; congenital lesions in 7 patients; cerebral tumors (meningioma, epipharynx carcinoma, germinoma, rhabdomyosarcoma, and medulloblastoma) in 7 patients; Sheehan's disease in 2 patients; trauma in 2 patients; and empty sella, meningitis, histiocytosis X, and agenesis of the septum pellucidum each in 1 patient. Most patients had been treated surgically with or without subsequent radiation therapy. Duration of GH deficiency varied from 1–36 yr. All patients signed an informed consent to the protocol, which was approved by the University Hospital Ethical Committee.

Patients were treated with rhGH (Genotropin, Pharmacia-Upjohn; or Humatrope, Eli Lilly & Co.) in varying doses. The treatment goal was to achieve an IGF-I concentration falling within the age-corrected normal range (mean  $\pm$  2 SD) for our laboratory (11). To reach this goal, the rhGH dose was adjusted at every visit. The time interval between the visits was 6 months. Treatment duration was 24 months. Serum IGF-I values were measured every 6 months. GH was measured by direct RIA using the WHO standard for human GH 80/505. The interassay coefficient of variation (CV) was 9.2, 7.8, 5.0%, and 6.0% at GH concentrations of 4.7, 10.6, 20.8, and 53.5 mE/L (11). IGF-I was determined by an in-house RIA. The intra-assay CV, expressed as the relative duplicate CV at concentrations between 5 and 50 nmol/L, was 5.7%. The interassay CV was 9.4% at a level of 8.4 nmol/L, 4.1% at 29.8 nmol/L, and 6.5% at an IGF-I concentration of 41.7 nmol/L (17).

Responsivity to rhGH was defined as the quotient of the rhGH-induced  $\Delta$ IGF-I (nmol/L) and the dose (IU/day·kg) used in the same period. Or in formula: rhGH responsivity = ( $\Delta$ IGF-I (nmol/L)/dose (IU/day·kg)) ( $\Delta$ IGF-I = change of IGF-I from baseline; dose = dose used during the last 6 months).

### Statistics

Values mentioned are means  $\pm$  SEM, except for the age where mean  $\pm$  SD is used. The unpaired Student's *t* test was used to evaluate differences found between two groups.

## Results

### Serum GH and IGF-I levels before rhGH therapy

No difference in baseline- or arginine-stimulated serum GH levels could be demonstrated between GH-deficient men and women. In both men and women, basal GH levels were less than 2 mU/L. After arginine provocation a slight increase in GH concentration was seen in a minority of the patients (maximum serum GH concentration, 4 mU/L). Baseline serum IGF-I levels, however, were significantly lower in women than in men ( $8.8 \pm 0.1$  vs.  $12.2 \pm 1.0$  nmol/L,  $P < 0.01$ ). Women on estrogen substitution had similar IGF-I levels as those without sex steroid substitution. The same was true for men with or without androgen therapy.

### Effects of gender on rhGH dose, serum IGF-I concentration, and rhGH responsivity

*rhGH dose.* The rhGH dose per kg body weight (IU/day·kg) required in all women was significantly higher than that for men at all time intervals ( $P < 0.05$ – $0.01$ ). In men, both on and without androgen substitution, the dose required decreased over time, the difference between 6 months and 24 months being statistically significant ( $P < 0.05$ ), whereas it plateaued in women (Fig. 1).

After the titration phase, the daily rhGH dose required to normalize IGF-I levels in women, both on and without replacement therapy, remained virtually unchanged. In men, the dose required decreased over time, from  $1.73 \pm 0.16$  IU/day at  $t = 6$  months to  $1.31 \pm 0.23$  IU/day at  $t = 24$  months ( $P < 0.05$ ) (Fig. 1). Although the daily rhGH dose required to normalize IGF-I in women was higher than in men over the whole treatment period, the difference reached statistical significance only after 24 months of therapy ( $2.05 \pm 0.23$  IU/day for women against  $1.31 \pm 0.23$  IU/day for men;  $P < 0.05$ ).

*Serum IGF-I levels and rhGH responsivity.* As mentioned earlier, baseline serum IGF-I levels were significantly lower in women than in men ( $P < 0.01$ ). After starting rhGH treatment, IGF-I levels increased in both men and women (from baseline to 6 months,  $P < 0.01$ ). After this initial increase, however, no further rise occurred either in men or in women.

The increase in rhGH responsivity (*i.e.* the increase of IGF-I per dose rhGH corrected for weight) over time was more pronounced in men than in women, the difference being statistically significant ( $P < 0.05$  at  $t = 6$  and  $t = 24$  months and  $P < 0.01$  at 12 and 18 months) (Fig. 2) at all time intervals. This was due partly to the fact that rhGH responsivity virtually remained unchanged over time in women ( $P > 0.10$ ), but almost doubled in men (difference between  $t = 6$  and 18 months;  $P < 0.01$ ) (Fig. 2).

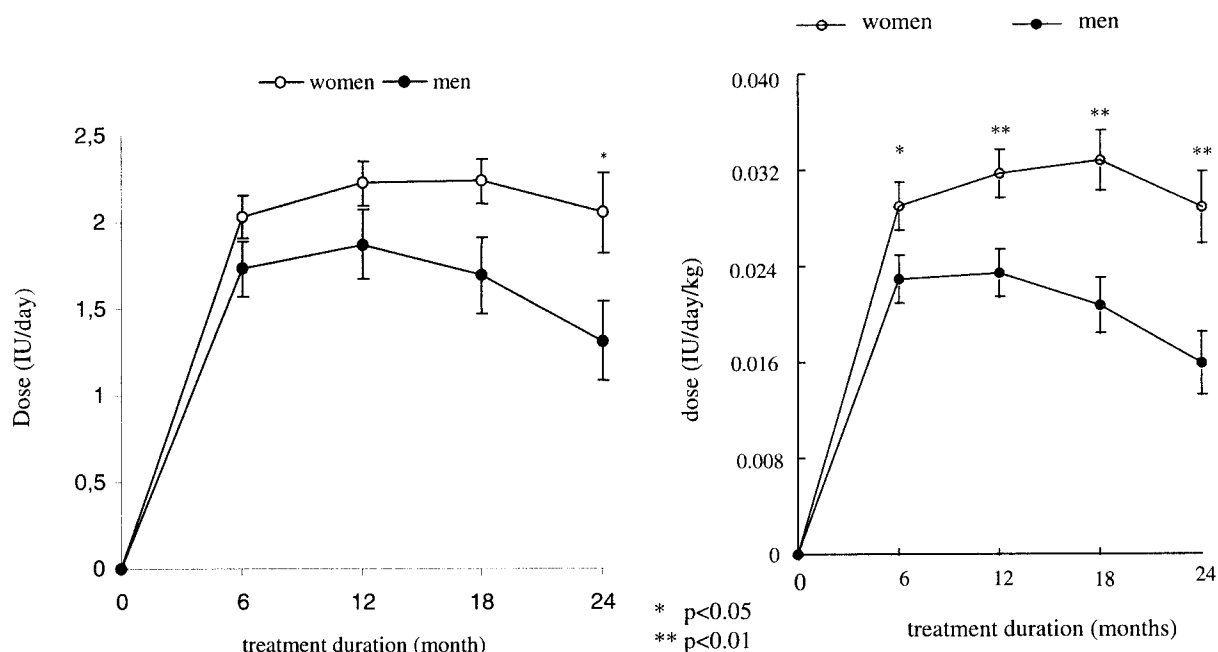


FIG. 1. Mean ( $\pm$ SEM) total daily rhGH dose and rhGH dose corrected for weight in GH-deficient men and women.

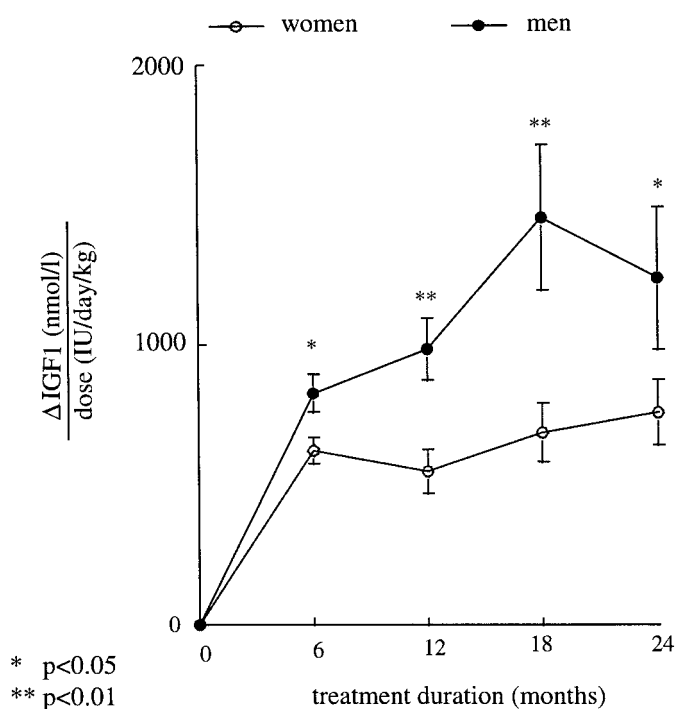


FIG. 2. Mean ( $\pm$ SEM) rhGH responsivity in GH-deficient men and women during treatment.

#### Effects of sex hormonal substitution on rhGH dose, serum IGF-I concentration, and rhGH responsivity

**Estrogen replacement in women: rhGH dose.** As mentioned earlier, 33 of 44 women received estrogen substitution (30 oral and 3 transdermal estrogen substitution) and 11 eugonadal women did not. Baseline IGF-I levels were virtually similar in both groups ( $9.4 \pm 0.9$  vs.  $7.0 \pm 1.6$  nmol/L,  $P > 0.10$ ). The weight-corrected rhGH dose required to achieve adequate

IGF-I levels was at all time intervals higher in the estrogen-treated women than in the women without estrogen substitution, but the difference was only statistically significant at 18 months ( $0.038 \pm 0.003$  vs.  $0.028 \pm 0.005$  IU/day·kg) and 24 months [ $0.033 \pm 0.001$  vs.  $0.024 \pm 0.001$  IU/day·kg ( $P < 0.05$ )].

After 6 months of treatment, the mean daily dose for women using estrogens was  $2.17 \pm 0.18$  IU/day and for women without estrogens was  $1.59 \pm 0.26$  IU/day, being statistically significant ( $P < 0.01$ ). During the whole treatment period of 24 months this difference remained statistically significant ( $P < 0.05$ ). At 24 months, the daily rhGH doses were  $2.50 \pm 0.25$  IU/day and  $1.50 \pm 0.18$  IU/day, respectively.

Exclusion of the data from the three women on transdermal estrogen replacement did not change the outcome of the analysis (data not shown).

**Serum IGF-I levels and rhGH responsivity.** In response to rhGH, serum IGF-I initially increased equally in both groups of estrogen-substituted and nonsubstituted women. From 6 months onward, however, IGF-I levels plateaued in the estrogen-substituted women, but increased in the women without estrogen, although this difference never reached statistical significance ( $P > 0.10$ ). At all time intervals from 12 months on there was a tendency ( $P < 0.10$ ) to lower IGF-I increments in the estrogen-treated group.

The difference in rhGH responsivity between substituted and nonsubstituted women was statistically significant ( $P < 0.01$  both at 18 and 24 months). In women without estrogen substitution, responsivity to rhGH almost doubled over time ( $P < 0.05$  for the change from  $t = 6$  months to  $t = 24$  months). In the women on estrogen substitution the rhGH responsivity plateaued from 6 months on (Fig. 3).

Again the exclusion of the data from the three women on

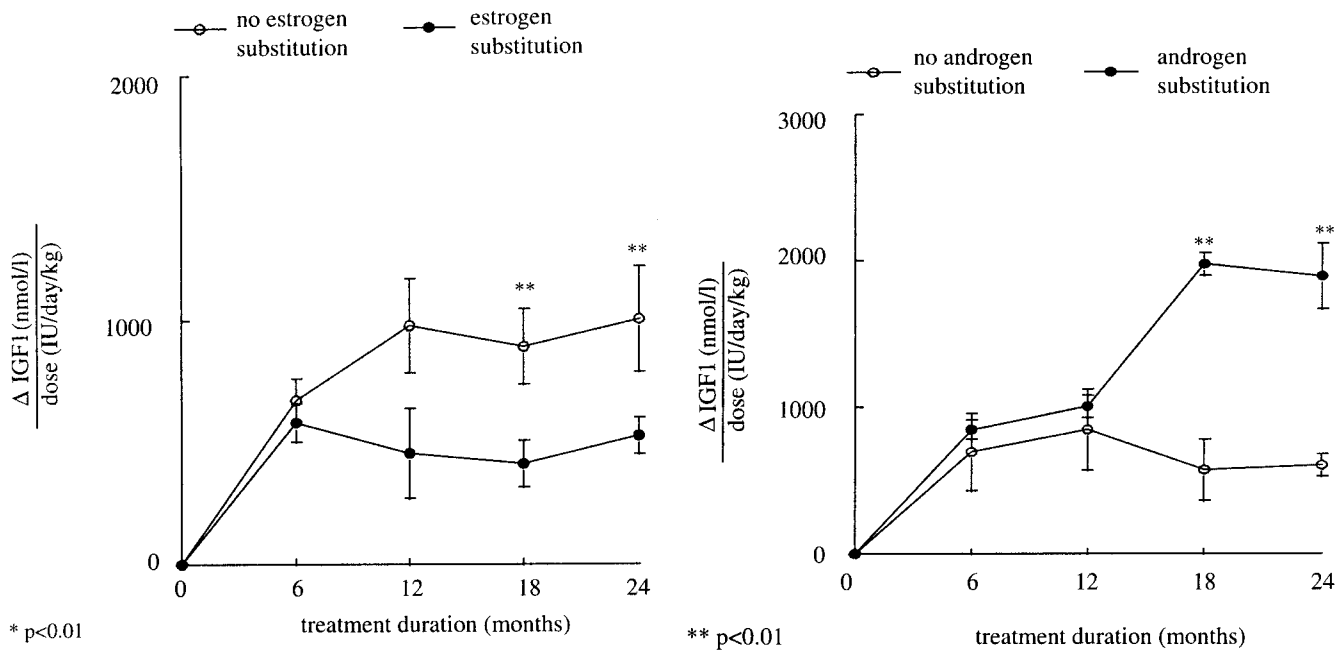


FIG. 3. Mean ( $\pm$ SEM) rhGH responsivity in GH-deficient women and men with and without sex hormone substitution.

transdermal estrogen replacement did not change the outcome of the analysis (data not shown).

*Androgen replacement in men: rhGH-dose.* After 6, 12, 18, and 24 months of treatment, the daily rhGH dose per kg body weight required to achieve adequate IGF-I levels was not statistically significant different between men with and without testosterone replacement. The same holds for the daily doses of rhGH in both groups of men (data not shown).

Baseline serum IGF-I levels in both groups were similar ( $12.0 \pm 1.0$  nmol/L in the androgen-substituted men *vs.*  $12.9 \pm 2.3$  nmol/L in the eugonadal men ( $P > 0.10$ )).

rhGH responsivity, however, doubled over time in the androgen-substituted group of men (increase from 6–24 months,  $P < 0.01$ ), not in the men without androgen substitution, reflecting an increase of rhGH responsivity by exogenous androgen therapy during continued rhGH administration (Fig. 3).

### Discussion

The present study revealed an overt sex difference in rhGH requirement in GH-deficient adults, persisting for 24 months. To achieve similar IGF-I increments, higher rhGH doses were needed in women than in men. This gender difference was even more pronounced as GH-deficient men achieved higher IGF-I increments than women at lower daily rhGH doses corrected for weight. Using standardized rhGH doses for GH-deficient women and men, Burman, *et al.* (13) found a similar sex difference in IGF-I responsivity to rhGH in GH-deficient adults, treated for 9 months. This gender difference in IGF-I responsivity was accompanied by a more pronounced loss of body fat, fall in total and low-density lipoprotein cholesterol, and in bone turn over in men than in women on rhGH therapy (13). Very recently Drake *et al.* (15) also reported a gender difference in IGF-I responsivity to

rhGH in GH-deficient adults treated for 3 months, the daily dose being 50% higher in females than in males. The time to achieve the maintenance dose was also significantly longer in women. The data in the present study indicate that the gender difference in rhGH requirement persists even after 24 months of rhGH treatment.

Obviously differences in estrogen concentrations have been incriminated as a possible underlying cause for the gender difference in rhGH requirement. Estrogens reportedly have distinct effects on the somatotrophic axis (compare *Introduction*). A reduction in IGF-I levels during oral estrogen replacement has been observed in healthy postmenopausal women (18), whereas Holloway *et al.* (19) found a blunted effect of rhGH on metabolic indices and body composition changes in healthy postmenopausal women receiving estrogens as compared with women without estrogen substitution. These data are in line with the idea that due to a first pass effect of estrogens the IGF-I synthesis in the liver is diminished. Indeed, after estrogen administration, a decrease in the expression of GH receptor gene and IGF-I messenger RNA has been found in laboratory animal hepatocytes (20, 21). Therefore, it was remarkable that in contrast to healthy women Burman *et al.* (13), in a rather small group of adult GH-deficient women with ( $n = 8$ ) and without ( $n = 7$ ) estrogen replacement, did not find a difference in rhGH-induced IGF-I concentration between both groups. After 3 months of treatment, Drake *et al.* (15) also failed to demonstrate such a difference both in median rhGH doses and IGF-I increment in response to rhGH in GH-deficient women subdivided by gonadal status and use of estrogen replacement.

In contrast, in the present study in a larger group of GH-deficient adults treated for a longer period of 24 months, an overall difference in IGF-I responsivity to rhGH was found between women with and without estrogen replacement.

Estrogen significantly blunted the IGF-I response to rhGH, IGF-I levels plateauing from 6 months on after the initial increase. The discrepancy of our results with those of both other studies may reside in the longer treatment period and the larger number of GH-deficient women in our study.

In our cohort of adult GH-deficient males, the group not receiving androgen replacement had lower rhGH responsiveness than men on androgen replacement over the whole time period. At 18 months and 24 months the difference was statistically significant. Unlike estrogen replacement in women, which blunted the IGF-I response to rhGH, in the androgen-treated males a steady increase in IGF-I responsiveness was observed over the 24-month treatment period, compatible with an androgen-induced rise in rhGH responsiveness over time induced by exogenous androgens. This finding is in line with observations of other authors reporting increases in circulating IGF-I levels in response to androgens in eugonadal men (12), hypogonadal men (22), and in boys with delayed puberty (23, 24). The changes in rhGH responsiveness over time in men and women as mentioned above indicate that there is a risk of overtreatment of men, especially men on sex hormone replacement, and undertreatment of women, especially women on estrogen substitution. The mechanism by which androgens increase IGF-I responsiveness to rhGH are not known. In castrated rabbits the expression of the GH receptor gene in the liver not only has been reported to decrease after estrogens, but rather to increase after testosterone.

Summarizing, a gender difference in rhGH dose requirement and IGF-I responsiveness to rhGH in GH-deficient adults was observed in line with recent literature. The present study further extends these data, demonstrating that this gender difference persists after longer times of rhGH therapy (24 months) and that estrogen replacement in GH-deficient women blunts the IGF-I response to rhGH, whereas in men androgens increase the responsiveness to rhGH over time. This may be associated with a risk of overtreatment of men, especially those on androgen substitution, and undertreatment of women, especially those on estrogen substitution.

### References

- Pieters GFFM, Smals AGH, Kloppenborg PWC. 1980 Defective suppression of growth hormone after oral glucose loading in adolescence. *J Clin Endocrinol Metab.* 51:265–270.
- Ho KY, Evans WS, Blizzard RM, et al. 1987 Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations. *J Clin Endocrinol Metab.* 64:51–58.
- Frantz AG, Rabkin MT. 1965 Effects of estrogen and sex difference on secretion of human growth hormone. *J Clin Endocrinol Metab.* 25:1470–1480.
- van den Berg G, Veldhuis JD, Frölich M, Roelfsema F. 1997 An amplitude-specific divergence in the pulsatile mode of growth hormone secretion underlies the gender difference in mean GH concentrations in men and premenopausal women. *J Clin Endocrinol Metab.* 81:2460–2467.
- Dawson-Huges B, Stern D, Goldman J, Reichlin S. 1986 Regulation of growth hormone and somatomedin C secretion in postmenopausal women: effect of physiological estrogen replacement therapy. *J Clin Endocrinol Metab.* 63:424–432.
- Diamond MP, Jones T, Caprio S, et al. 1993 Gender influences counterregulatory hormone response to hypoglycemia. *Metabolism.* 42:1568–1572.
- Kerrigan JR, Rogol AD. 1994 The impact of gonadal steroid hormone action on growth hormone secretion during childhood and adolescence *Endocr Rev.* 13:281–298.
- Faria ACS, Berkenstein LW, Booth Jr RA, et al. 1992 Pulsatile growth hormone release in normal women during the menstrual cycle. *Clin Endocrinol (Oxf).* 35:591–596.
- Bellantoni MF, Vittone J, Campfield AT, et al. 1996 Effects of oral vs. transdermal estrogen on the growth hormone/insulin-like growth factor I axis in younger and older postmenopausal women: a clinical research center study. *J Clin Endocrinol Metab.* 81:2848–2853.
- Juul A, Main K, Blum WF, Lindholm J, Ranke MB, Skakkebaek NE. 1994 The ratio between serum levels of insulin like growth factor (IGF)-I and the IGF binding proteins (IGFBP-1,2 and 3) decreases with age in healthy adults and is increased in acromegalic patients. *Clin Endocrinol.* 41:85–93.
- Span JPT, Pieters GFFM, Sweep CGJ, et al. 1999 Plasma IGFI is a useful marker of growth hormone deficiency in adults. *J Endocrinol Invest.* 22:446–450.
- Hobbs CJ, Plymate SR, Rosen CJ, Adler RA. 1993 Testosterone administration increases insulin-like growth factor-I levels in normal men. *J Clin Endocrinol Metab.* 77:776–779.
- Burman P, Johansson AG, Siebahn A, Vessby B, Karlsson FA. 1997 Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. *J Clin Endocrinol Metab.* 82:550–554.
- Janssen YJH, Frölich M, Roelfsema F. 1997 A low starting dose of genotropin in growth hormone deficient adults. *J Clin Endocrinol Metab.* 82:129–135.
- Drake WM, Coyte D, Camacho-Hübner C, et al. 1998 Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults. *J Clin Endocrinol Metab.* 83:3913–3919.
- Jorgensen JOL, Thuesen L, Ingemann-Hansen T, et al. 1989 Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet.* i:1221–1225.
- Pieters GFFM, Romeyn JE, Smals AGH, Kloppenborg PWC. 1982 Somatostatin sensitivity and growth hormone responses to releasing hormones and bromocryptine in acromegaly. *J Clin Endocrinol Metab.* 54:942–947.
- Ho KKY, O'Sullivan AJ. 1997 Oestrogen regulation of growth hormone action. In: Lanberts SWJ, ed. *The diagnosis and treatment of pituitary insufficiency.* Bristol; 143–159.
- Holloway L, Butterfield G, Hintz RL, Gesundheit N, Marcus R. 1994 Effects of recombinant human growth hormone on metabolic indices, body composition, and bone turnover in healthy elderly women. *J Clin Endocrinol Metab.* 79:470–479.
- Yu YM, Domené HM, Sztejn J, Counts DR, Cassorla F. 1996 Developmental changes and differential regulation by testosterone and oestradiol of growth hormone receptor expression in the rabbit. *Eur J Endocrinol.* 135:583–589.
- Krattenmacher R, Knauth R, Parczyk K, Walker A, Hilgenfeldt U, Fritzsche KH. 1994 Estrogen action on hepatic synthesis of angiotensinogen and IGF-I: direct and indirect estrogen effects. *J Steroid Biochem Mol Biol.* 48:207–214.
- Hoffman DM, O'Sullivan AJ, Freund J, Ho KK. 1995 Adults with growth hormone deficiency have abnormal body composition but normal energy metabolism. *J Clin Endocrinol Metab.* 80:72–77.
- Soliman AT, Khadir MM, Asfour M. 1995 Testosterone treatment in adolescent boys with constitutional delay of growth and development. *Metabolism.* 44:1013–1015.
- Keenan BS, Richards GE, Mercado M, Dallas JS, Eakman GD, Baumann G. 1996 Androgen regulation of growth hormone binding protein. *Metabolism.* 45:1521–1526.