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Growth Hormone Secretagogue Treatment in Hypogonadal Men Raises Serum Insulin-Like Growth Factor-1 Levels

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Abstract

Realizing the reported misuse of human growth hormone (GH), investigation of a safe alternative mechanism for increasing endogenous GH is needed. Several GH secretagogues are available, including GH-releasing peptides (GHRPs) GHRP-2 and GHRP-6, and the GH-releasing hormone analog, sermorelin (SERM). Insulin-like growth factor 1 (IGF-1) serves as a surrogate marker for GH. Here, the effect of GHRP/SERM therapy on IGF-1 levels is evaluated. A retrospective review of medical records was performed for 105 men on testosterone (T) therapy seeking increases in lean body mass and fat loss who were prescribed 100 mcg of GHRP-6, GHRP-2, and SERM three times daily. Compliance with therapy was assessed, and 14 men met strict inclusion criteria. Serum hormone levels of IGF-1, T, free T (FT), estradiol (E), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were evaluated. Mean (SD) age of the cohort was 33.2 (2.9) years, and baseline IGF-1 level was 159.5 (26.7) ng/mL. Mean (SD) duration of continuous GHRP/SERM treatment was 134 (88) days. Mean posttreatment IGF-1 level was 239.0 (54.6) ng/mL ($p < .0001$). Three of the 14 men were on an aromatase inhibitor and/or tamoxifen prior to treatment and another 4 men were coadministered an aromatase inhibitor and/or tamoxifen during treatment. Inhibition of E production or estrogen receptor blockade resulted in smaller increases in IGF-1 levels. GHRP/SERM therapy increases serum IGF-1 levels with strict compliance to thrice-daily dosing. The results suggest that combination therapy may be beneficial in men with wasting conditions that can improve with increased GH secretion.

Keywords

growth hormone–releasing peptides, growth hormone, growth hormone secretagogue, hypogonadism, IGF-1 levels

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Growth hormone (GH) increases lean body mass and reduces fat mass in adults, and increases exercise tolerance and maximum oxygen uptake (Carroll et al., 1998). Exogenous recombinant human growth hormone (hGH) has numerous potential risks, and its use is restricted by the U.S. Food and Drug Administration (FDA) to a discrete set of conditions ("Blue Cross Blue Shield Drug info," 2015; Carel et al., 2012; U.S. FDA, 2013). The safety concerns associated with exogenous GH use, however, may be mitigated by the use of GH secretagogues (GHSs), which stimulate endogenous GH production and maintain it within normal physiologic parameters (Bowers, 1998; Bowers, Laferrére, Hurley, Veldhuis, 2008; Smith, 2005).

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When administered continuously to humans, GHSs such as GH-releasing peptides (GHRPs) and GH-releasing hormone (GHRH) analogs elicit physiologic, pulsatile GH secretion (Bowers, 1998, 2008). GHRPs are short, ~6 amino acid peptides initially developed as opiate drug analogs, which stimulate GH release without affecting opiate receptor activity or levels of other pituitary hormones (Bowers, 1998). GHRP activity is independent from that of GHRH, as repeated injections of GHRPs desensitize the GH release response but do not alter the response when GHRH is given (Bowers, 1998). In fact, the most significant increases in natural GH release occur via synergistic action of GHRPs and GHRH acting at the GHS receptor (GHS-R) and GHRH receptor, respectively (Bowers, 1998; Smith, 2005; Smith et al., 1999).

The reported use of these peptides in humans is limited, but studies have demonstrated improvements in body mass and anti-catabolic effects by GHS-R agonists such as the novel oral compound MK-0677 (Murphy et al., 1998, 2001; Nass et al., 2008; Svensson et al., 1998). GHRP-2 has also shown promising anti-catabolic effects—a case report of GHRP-2 use in a patient with anorexia nervosa reported increased body weight, muscle, and fat mass (Haruta et al., 2015). A surrogate blood marker for GH in humans is insulin-like growth factor 1 (IGF-1), which due to its 18-hour half-life (in contrast with the 3- to 4-minute half-life of GH) is a more consistent marker of GH levels (Guler, Zapf, Schmid, & Froesch, 1989; Hartman et al., 1991). IGF-1 levels correlate with circulating GH levels (Furlanetto, Underwood, Van Wyk, & D'Ercole, 1977). In evaluating the impact of GHRP-2 on IGF-1 levels, a small study examining the effects of daily 100-mcg injections of GHRP-2 for 5 days in nine healthy young men failed to demonstrate increases in IGF-1 (Nijland, Strasburger, Popp-Snijders, van der Wal, & van der Veen, 1998). In contrast, in a cohort of 26 critically ill patients, a 21-hour infusion of GHRP-2 and GHRH resulted in a significant rise in IGF-1 levels (Van den Berghe et al., 1997). Neither study considered pulsatile stimulation of GH secretion, which is essential for IGF-1 production as well as the tissue effects of GH (Jorgensen, Moller, Lauritzen, & Christiansen, 1990). A study of four men and two women with GH deficiency demonstrated that more frequent GH dosing without a change in total dose raised IGF-1 levels, as eight smaller boluses or simultaneous continuous GH infusion were more effective in raising IGF-1 levels than two large bolus doses of GH alone (Jorgensen et al., 1990).

There are numerous GHSs currently available, although relatively few data exist examining the effects of GHSs on serum hormone and anthropomorphic parameters in men. In this study, the impact of a combination of GHRP-2, GHRP-6, and the GHRH agonist sermorelin (SERM) on serum hormone and IGF-1 levels in men on testosterone (T) therapy is evaluated.

Methods

Patient Cohort

With institutional review board (IRB) approval, a retrospective review of medical records was performed for 105 hypogonadal men on T therapy seeking gains in lean body mass and fat loss who were prescribed a combination of GHRP-6, GHRP-2, and SERM. All patients were started on therapy between 2012 and 2015 at a dose of 100 mcg of each compound, injected subcutaneously three times daily. To be included in the study, compliance with treatment was required, which was assessed via frequency of prescription fills. Men refilling their GHS prescriptions within 45 days for each month's supply of drug were considered compliant. Men with baseline IGF-1 levels of <200 ng/mL were included, and men with IGF-1 levels >200 ng/mL excluded. Of the 105 initial men whose data were reviewed, 14 men met the above inclusion criteria and were included in the analysis.

Baseline serum hormone levels, including IGF-1, T, free T (FT), estradiol (E), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), were determined prior to therapy initiation and at each follow-up appointment approximately every 3 to 4 months during treatment. All laboratory testing was performed by the Laboratory for Male Reproductive Research and Testing at Baylor College of Medicine.

Statistical Analysis

Data were analyzed using Microsoft Office Excel (Microsoft, Redmond, WA). Data parametricity was assessed using histogram analysis and statistical comparisons between baseline and treatment hormone levels performed using two-tailed Student's *t*-test, with a p value <.05 considered significant.

Results

Fourteen hypogonadal men on T therapy with baseline IGF-1 levels <200 ng/mL were treated with GHRP-6, GHRP-2, and SERM three times daily at a dose of 100 mcg of each compound delivered via subcutaneous injection (Table 1). Mean (SD) age within the cohort was 33.2 (2.9; range 29–39) years. Baseline mean (SD) hormone levels were IGF-1 159.5 (26.7; range 97–195) ng/mL, T 586.9 (550.5; range 76–1640) ng/dL, FT 12.9 (11.8; range 2.2–36.7) ng/dL, FSH 1.1 (1.9; range 0.02–7) mIU/mL, LH 1.1 (1.4; range 0.02–4) mIU/mL, and E 5.5 (9.0; range 2–38) ng/dL. Mean (SD) duration of GHRP-6/GHRP-2/SERM treatment was 134 (88) days. Significant increases in IGF-1 levels were observed at all follow-up intervals (Table 2 and Figure 1). Significant increases in T and FT levels were also observed starting at 90 days of follow-up. No significant

Table 1. Patient Demographics at Baseline.

	Mean (SD)	Range	*n*
Age (years)	33.2 (2.9)	29–39	14
Height (inches)	72.5 (3.2)	63–75	12
Weight (lb)	196 (35)	145–280	12
Fat percentage (%)	12 (2.1)	9–15	11

Comorbidity	*n* (%)
Diabetes mellitus	0 (0)
Hypertension	1 (7)
Hyperlipidemia	0 (0)
Coronary artery disease	0 (0)
Current or former smoker	4 (29)
Hypothyroidism	1 (7)

Table 2. Effects of GHS Treatment on Serum Hormone Levels.

	Follow-up interval			
Variable	Baseline (*n* = 14)	1–90 Days (*n* = 8)	91–180 Days (*n* = 5)	181–270 Days (*n* = 4)
IGF-1 (ng/mL)	159.5 (26.7)	263.8* (41.1)	196.8* (40.5)	253.3* (50.6)
T (ng/dL)	586.9 (550.5)	1035.1 (455.6)	1326.0* (485.7)	1060.3* (508.5)
Free T (ng/dL)	12.9 (11.8)	22.2 (9.9)	36.6* (15.0)	23.6 (6.7)
FSH (mIU/mL)	1.1 (1.9)	0.2 (0.3)	0.2 (0.09)	0.3 (0.3)
LH (mIU/mL)	1.1 (1.4)	0.2 (0.3)	0.3 (0.2)	0.2 (0.07)
E (ng/dL)	5.5 (9.0)	6.8 (5.5)	7.4 (5.9)	2.5 (1.0)

Note. Values are presented as mean (SD). E = estradiol; FSH = follicle-stimulating hormone; GHS = growth hormone secretagogue; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; T = testosterone.
*$p < .05$.

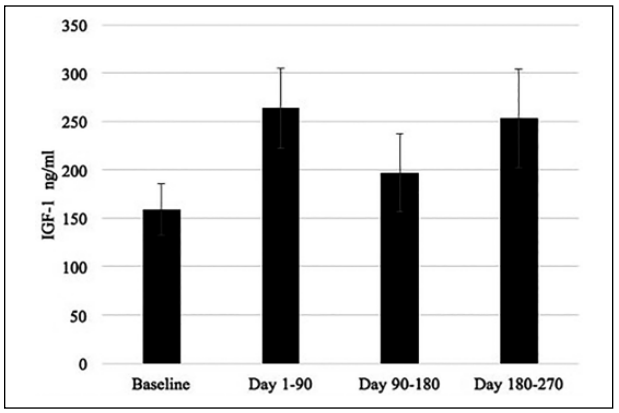

Figure 1. Effects of GHS treatment on IGF-1 levels. GHS = growth hormone secretagogue; IGF-1 = insulin-like growth factor 1.

changes in LH, FSH, or E levels were observed at any point during follow-up. Anthropomorphic data were not available for the majority of men on follow-up.

Table 3. Effect of Antiestrogens on GHS Stimulation of IGF-1.

IGF-1 (ng/mL)	Mean (SD)	Range	*n*
Baseline	159.5 (26.7)	97–195	14
Treatment + anti-E	217.6 (42.9)	149–281	8
Treatment No anti-E	262.9 (48.8)	179–320	9

Note. E = estradiol; GHS = growth hormone secretagogue; IGF-1 = insulin-like growth factor 1.

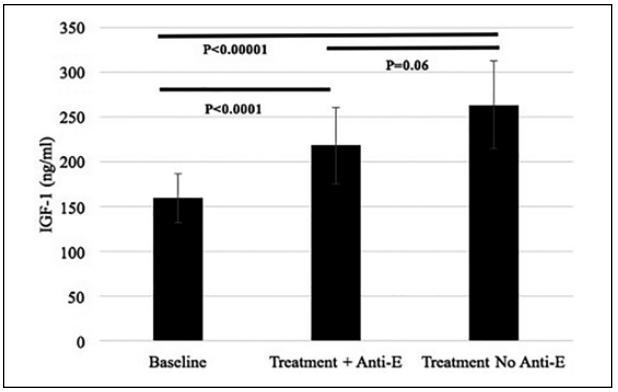

Figure 2. Estrogen receptor blockade on IGF-1 levels during GHS treatment. E = estradiol; GHS = growth hormone secretagogue; IGF-1 = insulin-like growth factor 1.

Three men began treatment with GHRP-6/GHRP-2/SERM while already on aromatase inhibitor or tamoxifen therapy for either gynecomastia or elevated E levels. During the treatment period, four more men were started on an aromatase inhibitor and/or tamoxifen for these indications, for a total of seven men on antiestrogen therapy during treatment follow-up. A trend toward significantly lower IGF-1 levels in men on antiestrogen therapy (217.6 [42.9] ng/mL) compared with men not on antiestrogens (262.8 [48.8] ng/mL, $p = .06$) was observed. Regardless of whether men were on antiestrogen therapy, a significant increase in IGF-1 levels was observed in both groups when compared with baseline (Table 3 and Figure 2).

Discussion

Exogenous hGH has numerous physiologic and anthropomorphic benefits, but its administration is strictly regulated by the FDA. Current indications for GH therapy in adults include (a) documented GH deficiency in childhood, (b) documented hypopituitarism as a result of pituitary or hypothalamic disease, surgery, radiation therapy, trauma, or aneurismal subarachnoid hemorrhage, (c) AIDS wasting syndrome, and (d) short bowel syndrome. Use of GH for anabolic therapy, except in the setting of AIDS, is not currently approved ("Blue Cross Blue Shield

Drug info," 2015). The strict indications for GH use are due in part to concerns over its safety (U.S. FDA, 2013). The "Safety and Appropriateness of GH treatments in Europe" (SAGhE) study, a long-term epidemiological study following European children treated with exogenous GH, observed a 30% increase in expected mortality in children taking GH. Specifically, higher mortality rates from bone malignancies, cardiovascular disease, and subarachnoid hemorrhage were identified (Carel et al., 2012). This increase in mortality, particularly due to malignancy, is thought to occur in patients with elevated IGF-1 levels (Cummings & Merriam, 2003; Isojima et al., 2012; Rosario, 2010). Of note, normal serum IGF-1 levels decrease in an age-dependent manner once a peak is reached during adolescence (Isojima et al., 2012; Rosario, 2010). In one study of prostate cancer risk in men with a mean age of 59.3 years, an IGF-1 level >294 ng/mL, which is above the upper limit of the normal reference range in the population (233 ng/mL), was associated with an increased risk of developing prostate cancer (Chan et al., 1998; Isojima et al., 2012).

GHSs can potentially provide similar benefits to those seen with the use of GH while avoiding the safety concerns associated with GH use, in part because GHSs can reproduce the physiologic pulsatility of GH secretion and limit GH and IGF-1 production to the normal physiologic range (Bowers, 2008; Smith, 2005). Due to the relatively recent clinical use of GHSs for changes in lean body mass and anti-catabolic effects, longer-term safety data paralleling those from GH studies are lacking. Safety studies performed using MK-0677 established an excellent safety profile en route to clinical development (Smith, 2005). MK-0677 had relatively few and mild adverse events such as dizziness, stomachache, and transient increases in aspartate transaminase (AST)/alanine transaminase (ALT) in trials in healthy young men, obese men, elderly men and women, and osteoporotic women (Chapman et al., 1996; Murphy et al., 1998, 2001; Svensson et al., 1998). Safety concerns relating to an increased incidence of congestive heart failure (CHF; 4 in the treatment group vs. 1 in the placebo group) was seen in one trial of MK-0677 in patients above 60 years of age with hip fracture (Adunsky et al., 2011). Another trial with 25% more participants and a comparable subject pool and study design did not identify adverse drug effects related to CHF, and treatment was well tolerated (Bach et al., 2004). The relatively small sample sizes of these studies may limit our understanding of the adverse effects of MK-0677.

MK-0677 raises serum IGF-1 levels in both beagles and humans (Chapman et al., 1996; Hickey et al., 1997; Smith, 2005). The drug also increases lean mass in obese males and the elderly, increases bone density in osteoporotic women, and has anti-catabolic effects in the setting of diet-induced nitrogen wasting (Murphy et al., 1998, 2001; Nass et al., 2008; Svensson et al., 1998). MK-0677 currently lacks FDA approval and is not yet commercially available, but other, not-yet FDA-approved GHSs are available for clinical use. In this study, a combination of GHRP-6, GHRP-2, and SERM, when used by healthy men seeking gains in lean body mass and fat loss and adhering to a thrice-daily dosing regimen, resulted in increases in IGF-1 levels during the study period. Interestingly, concomitant use of a GHS and an antiestrogen resulted in smaller, but nevertheless significant, increases in IGF-1 levels. Previous studies have reported that estrogen stimulates GH secretion via feedforward drive by GHRH and GHRP, while also overcoming feedback restraint by somatostatin (Veldhuis & Bowers, 2003). Estrogen also regulates expression of the IGF-1 receptor in breast cancer cell lines, and antiestrogens mediate the effects of IGF-1 by downregulating the expression of IGF-1 receptor (Chalbos, Philips, Galtier, & Rochefort, 1993; Martin & Stoica, 2002; Winston, Kao, & Kiang, 1994). Thus, the clinical effects of antiestrogens on IGF-1 levels observed in the present study may be explained by these mechanisms.

Use of GHSs may be appropriate in clinical scenarios where exogenous GH may have demonstrated clinical benefit, such as wasting conditions and osteoporosis. GHSs may also facilitate treatment of GH deficiency, as intranasal GHRP-2 given twice daily restored normal growth rates in a study of 15 children with GH deficiency and short stature (Pihoker, Badger, Reynolds, & Bowers, 1997). In the study mentioned in the preceding text, GHRP-2 failed to provide "catch-up growth," and IGF-1 levels were not evaluated. However, the use of GHRP-2 could serve to limit the duration of GH use in children with GH deficiency, thus limiting the risks associated with GH use.

This study is limited by several factors. First, the relatively small and select patient cohort, retrospective nature, and short duration of the study limit the interpretation and generalizability of the results. Moreover, strict inclusion criteria were necessary to maintain high levels of GH over longer periods of time and to demonstrate that changes in IGF-1 levels were isolated to men who were strictly compliant with their GHS regimen and who presented with relatively low IGF-1 levels. Relatively low IGF-1 levels are important to the study criteria because the action of GHRPs and SERM are subject to regulatory feedback and are only designed to help the patient attain physiologic levels of IGF-1 (Bowers, 1998, 2008; Smith, 2005). Second, anthropomorphic data for the patient cohort were lacking, limiting the ability to determine the effects of GHSs on these variables, particularly body mass index and lean body mass. Third, while an effect of GHSs on IGF-1 levels was demonstrated, the direct

impact on GH levels was not assessed, in part due to the short half-life of GH and the retrospective nature of this study. Fourth, other end points, such as insulin tolerance and fasting glucose levels, which are adversely affected by MK-0677, were not evaluated in the current work (Nass et al., 2008; Svensson et al., 1998). Future work will reconcile these limitations.

Conclusion

Combination therapy with the GHSs GHRP-6, GHRP-2, and SERM increases serum IGF-1 levels with strict compliance to thrice-daily dosing. Increases in serum IGF-1 while on treatment approached the upper limits of the laboratory reference range (250 ng/mL), but were inhibited by blocking estrogen action. Taken together, the results suggest that combination therapy with GHRP-6, GHRP-2, and SERM may be beneficial in wasting conditions in which increases in fat-free mass are desirable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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