

The Effects of Growth Hormone and Sex Steroid on Lean Body Mass, Fat Mass, Muscle Strength, Cardiovascular Endurance and Adverse Events in Healthy Elderly Women and Men

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Key Words

Growth hormone · Testosterone · Oestrogen · Sex hormones · Elderly population · Lean body mass · Fat mass · Adverse events

Abstract

Decreases in growth hormone (GH) and insulin-like growth factor I occur with age, in addition to oestrogen deficiency in women and a reduction in the levels of testosterone in men. These age-related hormonal changes may contribute to reductions in lean body mass, muscle strength and cardiac endurance, which can be partially reversed in elderly people with GH treatment, and testosterone supplements and oestrogen/progestin hormone replacement therapy in men and women, respectively. These treatments are, however, thought to have potentially serious adverse effects. We conducted a study to evaluate the separate and interactive effects of GH and sex steroids on body composition, muscle strength and cardiac endurance as well as the rate of adverse events in healthy elderly people. The results of the study

showed that although there were beneficial effects with GH and sex steroid treatment, a high percentage of adverse effects occurred after 26 weeks of treatment, demonstrating a need for more research on the safety of hormonal therapy in the elderly population.

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Introduction

Decreases in growth hormone (GH) and circulating insulin-like growth factor I (IGF-I), oestrogen deficiency in women and diminished levels of testosterone in men occur during human ageing [1–3]. Evidence to date is consistent with the hypothesis that these age-related decreases in hormone balance and regulation contribute to the concomitant reductions in lean body mass (LBM), muscle strength and cardiac endurance, and increases in body fat observed with normal ageing [4–6]. The treatment of non-elderly GH-deficient adults with recombinant human GH (rhGH), hypogonadal men with testosterone and hypogonadal women with oestrogen/progestin hormone replacement therapy (HRT) can reverse or attenuate similar changes in body composition and function which are seen in these patients [7, 8].

A full report of these data appears in Blackman MR et al: JAMA 2002;288:2282–2292.

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0301-0163/03/0607-0121\$19.50/0

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Several reports indicating that rhGH or testosterone supplementation increases LBM and reduces body fat in elderly men have led to public interest in the use of rhGH to delay these (and other) effects of ageing [9–11]. The efficacy of these hormone interventions (either alone or in combination) to improve physiological and functional outcome measures remains uncertain. Moreover, GH treatment in adults, especially older adults, may be accompanied by adverse reactions such as carpal tunnel syndrome, fluid retention with peripheral oedema, joint pain and swelling, gynaecomastia, glucose intolerance and, possibly, increased risk of cancer [12–15]. Testosterone supplementation could potentially accelerate the growth of prostate cancer or hyperplasia, and there is concern regarding whether the effect of testosterone on the plasma lipid profile (lower high-density lipoprotein and/or increased low-density lipoprotein cholesterol) might promote the development of atherosclerosis. Even HRT in women has recently been called into question because of recent studies showing a lack of benefit for, and in some cases an increased risk of, cardiovascular disease and a greater risk of breast cancer [16]. The marketing of rhGH and other hormone supplements to lay persons often ignores the extent to which these adverse events may occur.

Study Design and Methods

We evaluated the separate and interactive effects of administration of rhGH and sex steroids on body composition, muscle strength and cardiac endurance. We also determined the rates of occurrence of adverse events during treatment in healthy, ambulatory, community-dwelling women ($n = 57$) and men ($n = 74$), aged between 65 and 88 years. The randomized, double-masked, placebo-controlled, non-crossover 26-week trial consisted of the following groups: rhGH (GH group), combined oestrogen/progestin (HRT group [women]), testosterone (T group [men]), rhGH plus sex steroid(s) (GH + HRT or GH + T) or placebo only (placebo group). We performed serial evaluations of serum levels of IGF-I, oestradiol (women only), testosterone (men only), and baseline and 26-week assessments of LBM and total fat mass by dual-energy X-ray absorptiometry, total muscle strength by isotonic 1-repetition maximum testing, and aerobic capacity by measurement of VO_2 max during graded treadmill exercise tests. Adverse effects were assessed at regular intervals using structured questionnaires, physical examination and laboratory tests, including measurements of

haematocrit, blood glucose and hormones. Six individuals (four women, two men) withdrew from the study before completing the full 26 weeks of treatment. Results of intent-to-treat analyses by analysis of variance in all participants randomized are reported below.

Results

In women, mean IGF-I levels rose after 26 weeks of treatment with GH ($p \leq 0.001$) or GH + HRT ($p \leq 0.05$), with no significant difference between those receiving GH alone and GH + HRT. In men, administration of GH or GH + T increased IGF-I levels ($p = 0.0001$) with no differences observed between the latter treatments. Administration of GH elicited a greater increase in IGF-I levels in men compared with women ($p \leq 0.01$). Administration of sex hormone(s) alone or with GH led to similar increases in serum oestradiol levels in women ($p \leq 0.0001$) and in serum testosterone levels in men ($p \leq 0.0005$).

As shown in figure 1a, LBM in men increased after administration of GH ($p < 0.0001$) and GH + T ($p < 0.0001$), but the increase did not reach significance with testosterone alone ($p = 0.06$). There was a greater increase in LBM after GH + T compared with GH alone ($p < 0.001$). In women, total LBM increased after administration of GH ($p < 0.001$) and GH + HRT ($p < 0.0001$), but not with HRT alone. Changes in LBM in the GH and GH + HRT groups did not differ from each other (fig. 1b). In men, fat mass decreased after administration of GH ($p < 0.0001$), and GH + T ($p < 0.0001$), but not with testosterone alone (fig. 1c). The fat mass decrease after administration of GH + T was greater ($p < 0.001$) than that after treatment with GH alone. In women, total fat mass decreased to a similar extent ($p < 0.001$) after administration of GH or GH + HRT, but not with HRT alone (fig. 1d). The only significant change in total body strength in men was a 6.8% increase in the GH + T group ($p < 0.05$). Strength did not change significantly in any female treatment group. In men, VO_2 max increased by 8.5% in the GH + T group ($p < 0.001$), whereas in women, VO_2 max/kg body weight did not increase significantly in any treatment group. Changes in LBM were positively and exponentially related to changes in total body strength ($r = 0.255$, $p < 0.005$) and in VO_2 max ($r = 0.324$, $p < 0.001$).

Significant incidences of oedema and arthralgias occurred in GH-treated women ($p < 0.05$), carpal tunnel symptoms were common in the GH + T group ($p < 0.05$)

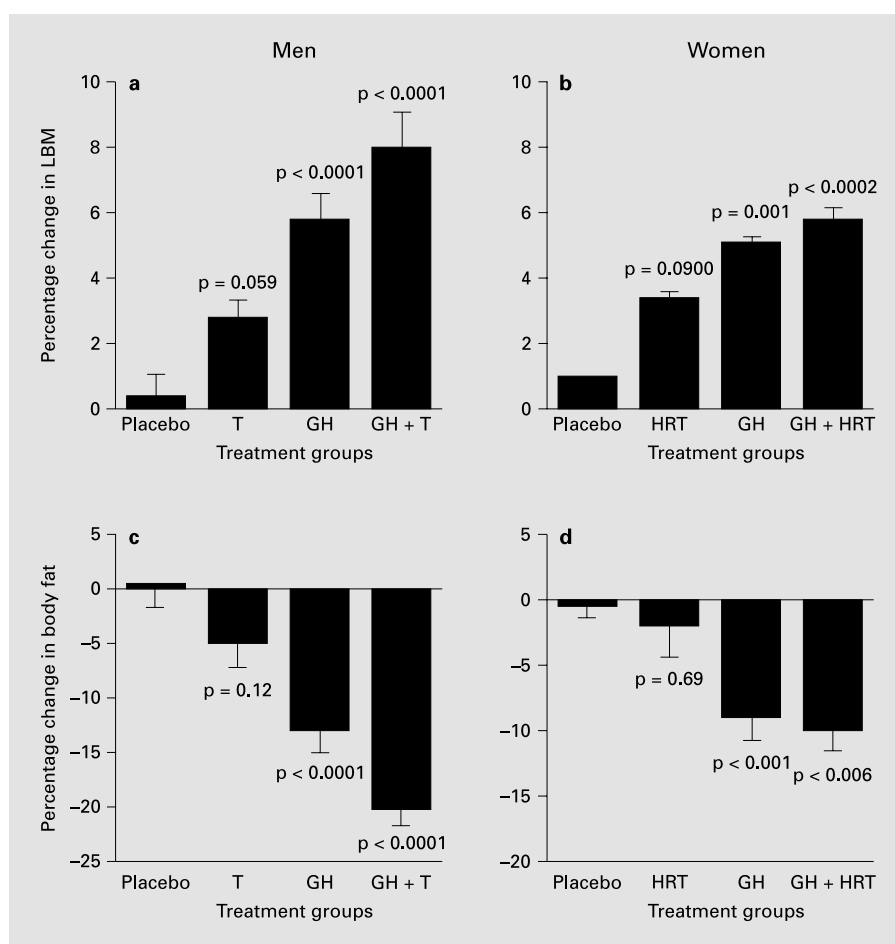


Fig. 1. Percentage changes in body composition variables in men (left) and women (right) after 26 weeks of hormone or placebo treatment. Bars have error bars at 1 standard deviation and p values vs placebo are shown above or below each bar. **a** Significant increases in LBM in men treated with GH and GH + T. **b** Significant increases in LBM in women treated with GH and GH + HRT. **c** Significant decreases in body fat mass in men treated with GH and GH + T. **d** Significant decreases in body fat mass in women treated with GH and GH + HRT.

and arthralgias were a significant complaint in GH-treated men ($p < 0.01$). Symptoms of oedema and carpal tunnel syndrome occurred at substantial, but non-significant, rates in women in the HRT group. Mean serum IGF-I level was correlated ($p < 0.05$) with the total number of GH-related adverse effects. No changes in body weight or blood pressure were observed. In women, the rate of new-onset glucose intolerance and diabetes mellitus did not occur, whereas six men developed diabetes, five of whom were receiving GH or GH + T ($p < 0.05$). At 26 weeks, serum glucose levels sampled following fasting, and at the 120-min time-point of a glucose tolerance test, showed significant increases compared with baseline tests in both men and women receiving rhGH. There were no significant increases in mean haematocrit values compared with placebo and no male participant had haematocrit values greater than 55% (i.e. polycythemia). Mean serum prostate-specific antigen [PSA] levels decreased in the GH-treated men ($p < 0.01$)

and were unchanged in the other groups, but two men in the testosterone group had increases in PSA of more than 1.0 ng/dl. Prostate symptom scores did not increase. Approximately 85% of the participants with GH-related adverse effects experienced relief after a 25% GH dose reduction. This study was too small and too short in duration to assess the effects of hormone treatments on the development of cancer or cardiovascular disease.

Discussion and Conclusion

Our findings suggest that GH and sex steroid supplementation, when given in combination to a carefully selected group of healthy elderly men and women, exert potentially beneficial effects on physiologically important outcome measures, such as body composition, and that an additive effect of GH and testosterone in men can improve muscle strength or aerobic capacity. Caution is war-

ranted, however, as a variety of adverse effects occurred in a high percentage of people after 26 weeks of doses of rhGH and testosterone or oestrogen, even though only physiological increases in serum IGF-I, testosterone or oestradiol were observed. Taken together, our data support the rationale for further investigations of the potential efficacy, safety and overall clinical utility of physiolog-

ical and targeted hormone-replacement paradigms in selected healthy and frail aged populations. Until more research, using a variety of treatment paradigms, has defined risk:benefit ratios better, however, the treatment of elderly men and women with rhGH should be confined to well-controlled research studies.

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