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Functional Consequences of the Somatopause and its Treatment

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The decline in the function of the growth hormone-releasing hormone, growth hormone, insulin-like growth factor (GHRH-GH-IGF) axis has been termed the somatopause. Many of the catabolic sequelae seen in normal aging has been attributed to this decrease in circulating GH and IGF-I. In order to provide hormone replacement therapy for the somatopause, elderly subjects have been treated with GH, IGF-I, or both hormones together. Whereas numerous beneficial effects on body composition, strength, and quality of life have been reported in some studies, other studies have reported only marginal functional improvements. Moreover, it is clear that both hormones can cause significant morbidity.

Key Words: GH; IGF-I; somatopause; body composition.

Introduction

GH secretion declines during aging *(1,2)* and there is a significant negative correlation between age and IGF-I, and a positive correlation between serum GH and IGF-I levels *(3)*. The authors have shown that the levels of the major serum IGF binding protein, insulin-like growth factor binding protein-3 (IGFBP-3), also decline in the elderly, and that elderly women with osteoporosis have lower IGF-I and IGFBP-3 levels than age-matched controls. It has been suggested that many of the catabolic changes seen in normal aging, including osteopenia and muscle atrophy, are in part caused by the decreased action of the GH/IGF-I axis (the somatopause).

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Somatopause and Cardiovascular Disease

In order to distinguish the direct effects of the somatopause from changes brought about by aging *per se*, it is instructive to study the pathophysiology of GH deficiency in hypopituitary young adults, who have the biochemical and hormonal manifestations of the somatopause without the attendant complications of other aging processes. GH deficient adults have an atherogenic lipid profile, with increased serum concentration of LDL cholesterol *(4)* and triglycerides, as well as increased plasminogen activator inhibitor activity and fibrinogen levels *(5)*. Premature atherosclerosis is common in hypopituitary adults, who also have decreased serum IGF-I levels *(6)*. The cardiovascular death rate in patients with hypopitu-itarism who had received hormone replacement therapy with thyroid hormone and adrenal and gonadal steroids, was nearly twice that of the general population *(7)*. This increased mortality may be a result of GH deficiency and the hypercholesterolemia which commonly accompanies it.

The authors studied the GH-IGF axis in elders by measuring serum IGF-I, IGF-II and IGFBP-3 levels as indices of integrated GH secretion to examine their relationship with blood lipid levels. One hundred thirty five healthy elderly subjects (60–91 yr) were studied. Men had significantly lower levels of IGFBP-3, high-density lipoprotein (HDL), and Apo-A1 compared to women. Using linear regression analysis, the authors observed an inverse relationship between age and IGF-I and IGFBP-3. Univariate regression analysis showed a strong and positive correlation of both IGF-I and IGFBP-3 with HDL-c and Apo-A1. These correlations were independent of age and the other lipid parameters. These data demonstrate that even in an elderly population, further aging is accompanied by a progressive decline in circulating IGF-I, IGF-II, and IGFBP-3, suggesting a continuing diminution of GH secretion throughout aging. Moreover, the strong correlation between HDL-c and a indices of GH secretion, suggests

that GH might play an important salutary role in lipid metabolism in healthy elderly subjects.

Finally, GH deficiency is associated with decreased ventricular mass and a hypokinetic syndrome with impaired cardiac performance and a low heart rate *(8)*. Thus, these data suggest that the somatopause may be implicated in the increased incidence of cardiovascular disease associated with aging, but the long term cardiovascular effects of GH/IGF-I therapy in the somatopause remain unclear.

GH-IGF-I Axis and Body Composition in the Elderly

Elderly men and women have increased fat mass and decreased lean body mass (LBM). The reduced LBM represents a loss of skeletal muscle, and is accompanied by decreased muscular strength and endurance. GH stimulates muscle protein synthesis in normal humans in vivo *(9)* and IGF-I induces myofiber hypertrophy in vitro *(10)*. Muscle strength is a significant predictor of bone mineral density *(11,12)* and of the risk of falling in elders *(13)*, and it is likely an important determinant of hip fracture risk. Thus an important strategy for diminishing hip fractures is to develop means to increase muscle strength *(14)*. Older men and women *(15)* are able to gain muscle strength and they retain the capacity for fiber hypertrophy with resistance training *(16)*. However, the magnitude of the hypertrophy response in elders is relatively small compared to younger individuals engaged in comparable training *(17)* During resistance exercise, GH levels rise quickly in young, but not elderly subjects *(18)*. In the elderly, plasma IGF-I levels are positively correlated with grip strength *(19)*. We have shown that GH therapy alone does not enhance strength gains achieved with resistance exercise in elderly men *(20)*. In elderly women undergoing a diet and exercise regimen, neither GH, IGF-I, or both hormones together had any effect on muscle strength or ventilatory capacity maximum.

GH infusions enhance amino acid uptake, indicating stimulation of new protein synthesis *(21)*. The authors have directly shown that net whole body and muscle protein synthesis increase with GH and IGF-I treatment in elderly women (22). They observed no change in muscle IGF mRNA in elderly men who received GH therapy *(20)*.

Aging also results in an increase in fat mass with concomitant increases in triglyceride (TG) turnover and circulating free fatty acids (FFA) and a decreased response to the lipolytic effects of insulin, *(23)* possibly contributing to the incidence of cardiovascular disease. GH has long been known as a regulator of lipid metabolism in humans. GH treatment of GH-deficient individuals is accompanied by an increase in plasma FFA concentration, and in FFA uptake as well as a decrease in lipoprotein lipase activity in subcutaneous abdominal and gluteal adipose tissue, *(24,25)* suggesting an increase in lipolysis and a decrease in lipogenesis.

GH Therapy in Elderly Subjects

Marcus et al. *(26)* gave GH to 12 elderly subjects, and circulating IGF-I levels increased rapidly. Subjects consumed a standardized diet, yet urinary nitrogen excretion decreased. There was a mild decrease in insulin sensitivity, but serum cholesterol levels fell. Rudman et al. *(27)* studied 21 men (ages 21–81) who had low serum IGF-I levels. GH treatment led to an 8.8% increase in LBM, a 14.4% decrease in adipose tissue mass, and a small (1.6%) increase in lumbar vertebral bone density. In 10 malnourished elderly (64-99 yr old) patients, 3 weeks of GH therapy led to an increase in mid-arm muscle circumference, body weight, and nitrogen retention *(28)*.

In a year long study of healthy older women, GH therapy maintained bone density at the hip, whereas placebo-treated women lost 1.5–3.0% over 15 mo, suggesting a protective, but not an enhancing effect of GH monotherapy. Of note, those women who were taking oral conjugated estrogens had a blunted response to GH therapy compared to those women who were not taking estrogen replacement therapy *(29)*.

It is likely that the results of the some previous studies were confounded by GH-dependent changes in body water compartments. All methods used for determination of body composition make the assumption that the composition of lean tissue is constant. The fluid accumulation implied by sodium retention could alter tissue composition, rendering this assumption, and thus the methods of body composition determination, invalid. As we have shown, anabolic hormones can cause shifts of water into cells and confound simplistic measures of body composition *(30)*. In all of the authors' subsequent studies, therefore, they have used multiple methods to estimate changes in body water compartments.

IGF-I Therapy in Elderly Women

The authors have previously demonstrated the safety of repeated injections of IGF-I in both the young and the elderly *(31)*. In contrast to GH treatment, IGF-I decreases plasma glucose in normals *(32)* and in diabetics *(33)*. Moreover, IGF-I infusions can attenuate the catabolic states induced by diet *(34)* and, as the authors have previously shown, by AIDS *(35)*. However, these latter metabolic effects were relatively modest. Clemmons and colleagues *(36)* demonstrated a marked enhancement of anabolism when both GH and IGF-I are used simultaneously. The anabolic action was greater than that seen with either agent alone, suggesting that combination GH + IGF-I therapy may have important therapeutic applications. In a recent study of patients who were on a diet and exercise regimen who were also treated with GH, IGF-I, or both hormones, the authors showed that fat mass decreased dramatically in patients who were treated with GH + IGF-I compared to either hormone alone, indicating a potential

role for combination therapy. However, the incidence of side-effects was also greater in those subjects receiving combination therapy.

The authors have also evaluated the effects of IGF-I and GH on calciotropic hormones and bone turnover markers *(37)*. Specimens were collected for 6 consecutive d before initiating hormone therapy. Resorption markers included urine hydroxyproline (OHP) and total pyridinolines (PYD); formation markers included osteocalcin, skeletal alkaline phosphatase (sALP), and type I pro-collagen carboxyterminal extension peptide (CICP). With GH and high-dose IGF-I, resorption and formation markers increased progressively to maximum levels at d 21. For GH, the percent increase in day 21 PYD, osteocalcin, and CICP = 143 ± 45, 53 ± 24, and 81 ± 30, respectively, $p <$ .06 -.02. For high-dose IGF-I, these increases = 108 ± 19, 77 ± 14, and 111 ± 32, $p <$ .02 -.002. However, with low-dose IGF-I, osteocalcin and CICP increased progressively (d 21% increases = 88 ± 51, 36 ± 14), but no change was observed in resorption markers. These results indicate that both GH and high-dose IGF-I increase the birthrate of remodeling osteons. By contrast, low-dose IGF-I may directly increase osteoblastic function without increasing bone resorption, and may, therefore, provide a useful means to increase bone mass. In a more recent study, the authors have shown that 15 µg/kg/d of IGF-I continued to increase markers of bone formation without altering markers of bone resorption for 12 wk.

Conclusion

As the activity of the GH/IGF-I axis declines with aging, elders suffer from a syndrome that has been termed the somatopause. LBM is diminished, adiposity increases and osteopenia develops. Physiologic GH/IGF-I replacement therapy, however, may reverse or prevent some of these inevitable sequelae of aging. However, reports of efficacy are conflicting, and therapy can be accompanied by significant side effects. Long-term studies utilizing low doses of IGF-I will be needed to elucidate the role of this growth factor as hormone replacement therapy for the somatopause.

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