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# Role of IGF-I in Muscular Atrophy of Aging

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**Loss of muscle mass and strength are well-known consequences of aging. The growth hormone/IGF-I pathway is both impaired with aging and essential for growth and maintenance of skeletal muscle. Despite this, growth hormone (GH) replacement has not been effective in increasing muscle mass and strength in the elderly. Possible explanations for this failure include**

1. **The presence of other age-related impairments in muscle that prevent the actions of GH and IGF-I and**
2. **Complications arising from a failure to deliver GH and IGF-I in the physiologically correct manner.**

**This article summarizes the results of clinical trials of GH and IGF-I in the elderly and discusses the current status of strategies for safely and effectively stimulating the GH/IGF-I pathway in this population.**

**Key Words:** Growth hormone; insulin-like growth factor I; aging; sarcopenia.

## Introduction

After the initial findings of Rudman et al. *(1)*, there was optimism for the use of growth hormone (GH) in reversing the losses in strength and functional independence that often accompany aging. Early studies reported that GH decreases fat mass and increases lean mass in elderly men. The drawbacks of GH therapy have now become clear. GH causes side effects, even at doses which do not excessively elevate insulin-like growth factor I (IGF-I) *(2)*, (*see* below). Although GH increases lean mass, it does not increase muscle mass or strength in the healthy elderly *(3)*. Furthermore, GH also fails to augment the strength gains obtained from exercise training in the healthy elderly *(4,5)*.

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These findings lead us to reconsider the following questions. First, do changes in the GH/IGF-I pathway underlie the sarcopenia of aging? Second, can this pathway be stimulated safely in the elderly? Third, can this stimulation be accomplished in such a way as to increase strength either alone or in combination with exercise training?

## Do Changes in the GH/IGF Pathway Underlie Sarcopenia of Aging?

Circulating GH and IGF-I are required for growth in adolescence and for maintenance of muscle mass and strength in adulthood. Production of these hormones is highest during adolescence and is maintained at a somewhat lower level during adulthood. In senescence, there is a further decline in the production of GH and IGF-I. A subset of the elderly, especially men, have IGF-I levels low enough to indicate that GH secretion is virtually absent. Circulating IGF binding protein-3 (IGFBP-3) is the major carrier of IGF-I, and is also reduced with age *(6)*. There may also be age-induced alterations in the intramuscular GH/IGF-I pathway. The authors reported *(7)* that muscle IGFBP-2 and IGFBP-3 are elevated in senescent rats, but this has not been assessed in humans to their knowledge.

Adult-onset hypopituitarism and senescence have some common features, including decreases in circulating peptides (GH and IGF-I) and decreases in muscle mass and strength. GH administration reverses some of these changes in adult hypopituitarism *(8)* this and this finding has led to the hypothesis that GH might produce similar changes in the elderly.

## Can the GH/IGF Pathway be Stimulated Safely in the Elderly?

GH causes a number of adverse effects which are summarized in Table 1. These side effects have not been explained and are seen with doses of GH which do not elevate IGF-I above the normal range for middle age. These side effects might result from the failure of GH administration to mimic the peaks and nadirs of natural

**Table 1**
Summary of Studies Evaluating the Effects of GH and IGF-I on Muscle

| Reference | Treatment | Findings | Side Effects |
|---|---|---|---|
| Rudman *(1)* | Healthy elderly men received 30 μg GH 3×/wk for 6 mo | Lean mass and skin thickness increased, fat mass decreased | Carpal tunnel syndrome<br>Gynecomastia<br>Hyperglycemia |
| Papadakis *(3)* | Healthy elderly men received 30 μg GH/kg 3×/wk for 6 mo GH | GH increased lean mass and bone mineral and decreased fat mass. GH did not increase strength of functional status | Edema, arthralgia |
| Taaffe *(5)* | Healthy elderly men underwent 24 wk of resistance training, receiving 20 μg GH daily during the last 10 wk | GH caused a trend toward a small increase in lean mass and decrease in fat mass. GH did not augment the exercise-induced strength increase | Fluid retention |
| Yarasheshki *(4)* | Healthy elderly men underwent 16 wk of resistance training ± 12.5 to 25 μg GH/kg daily | GH augmented exercise-induced increase in lean mass, but did not augment increases in strength and functional status. | Carpal tunnel syndrome<br>Arthralgia<br>Fluid retention |
| Thompson *(9)* | Healthy elderly women received 15 μg IGF-I/kg, b.i.d. for 4 wk | Decreased fat mass, trend to increased lean mass | Well-tolerated, 1 case of headache; side effects occurred at a higher dose |
| | 25 μg GH/kg daily | Increased lean mass, decreased fat mass, nitrogen retention | Lethargy, bloating, joint pain |
| Ghiron *(10)* | Healthy elderly women received 15 μg IGF-I/kg, b.i.d. for 4 wk | Increased markers of bone formation (osteocalcin) | None listed |
| | 25 μg GH/kg daily | Increased bone turnover and circulating IGFBP-3 | None listed |
| Cuneo *(11)* | GH-deficient adults (mean age 39) received 0.07 U/kg daily for 6 mo | Increases in muscle mass and strength were observed | None listed |

GH secretion. GH injections have typically been given three times per wk or daily. There are no studies where 24 h GH concentration curves are compared for natural secretion vs GH injection. However, it is probable that injection of GH matches neither the peaks nor the nadirs of natural secretion. Peak GH concentrations may be higher with injection because it is not distributed among several pulses of secretion per day as is natural secretion. Nadir GH concentrations may also be higher with injected GH because of the pharmacokinetics of absorption from the site of injection. Side effects might also result from the direct actions of GH, those not mediated by IGF-I. Lieberman et al. *(8)* reported that secretion of IGF-I in response to a single injection of GH, is blunted in the elderly. Thus, in the elderly, higher levels of GH may be required to stimulate sufficient IGF-I production.

Although there are fewer studies of IGF-I administration in the elderly, it appears that IGF-I may be better tolerated than GH. Thompson et al. *(9)* reported that a fairly low dose of IGF-I (30 μg/kg/d) was well-tolerated by healthy elderly women. A dose of GH that elevated IGF-I to a similar degree caused a much higher incidence of side

effects. Ghiron et al. *(10)* found this same dose of IGF-I to stimulate markers of bone formation. Although IGF-I can cause hypoglycemia when administered intravenously, this does not appear to be a problem following subcutaneous injection.

## Can the Stimulation of the GH/IGF Pathway Increase Strength in the Elderly?

The effects of GH and IGF-I on muscle in the elderly are summarized in Table 1. GH administration has not yet proven effective in increasing muscle mass or strength. The apparent increase in lean mass seen with GH administration probably represents a combination of fluid retention and increased nonmuscle protein, the latter in the form of a thickening of the skin and an increase in the size of some organs. However, the GH/IGF pathway is quite complex, consisting of numerous peptides with endocrine and autocrine actions. As a result, there are many possible strategies for stimulating the GH/IGF-I pathway. Treatments that need further study include IGF-I, either alone or in combination with GH or IGFBPs. There are several reasons for considering the combination of GH and IGF-I. The benefit of IGF-I would be that anabolic effects could be obtained, as well as avoiding a dose of GH high enough to cause adverse effects. The benefit of GH would lie in its direct effects, those not mediated by IGF-I. These include stimulation of IGFBP-3 production and increased glomerular filtration. Another reason for combining GH and IGF-I is that administration of IGF-I alone may suppress endogenous GH secretion. In addition, GH and IGF-I have greater anabolic actions in combination than does either agent alone. Thus, combination therapy might allow for greater anabolic action with fewer adverse effects.

It seems likely that a useful strategy for stimulating the GH/IGF pathway can be found, one which will restore muscle mass and strength to the frail elderly, with a minimum of side effects.

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