Is Growth Hormone an Anti-ageing Remedy?

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Growth Hormone and Ageing

Growth hormone (GH) is a peptide hormone secreted into the blood stream from the anterior pituitary gland in pulses, normally during sleep. The pulsatile release of GH is a result of the interacting stimulatory (by growth hormone releasing hormone (GHRH)) and inhibitory (by somatostatin (SS)) inputs from the hypothalamus, through the negative feedbacks of GH. GH mediates its physiological effects in the tissues through its direct peripheral action as well as indirectly via the serum insulin like growth factor I (IGF-I). The latter is secreted from the liver in response to GH stimulation. Apart from its important role in stimulating linear growth in childhood, GH has a number of metabolic effects that persist throughout life. GH is secreted throughout life. Circulating GH concentrations are maximal during the pubertal growth spurt but then decline with age. The mean daily GH secretion declines at an average rate of 14% per decade, and the mean 24-hour GH concentration is undetectable in 25% of normal elderly persons aged 50 years old and over. Serum GH level has a very short half-life, and a single measurement of serum GH level is difficult to interpret. The 24-hour GH secretion can reflect the GH secretory status. Alternatively, one can use the serum IGF-I level, as a surrogate index of GH-IGF-I axis sufficiency, as the serum IGF-I level has very little diurnal variations. By the young IGF-I standard, 80% of healthy old men are GH deficient. The GH secretory response to GH-RH is still preserved in healthy ageing. The responses of GH release to other stimuli are variably affected by ageing. The acute response to exercise is reduced, but the response to arginine, via inhibition of SS, is not affected. Moreover, the pituitary’s GH secretory response to GHRH and GH secretagogue (GHS) stimulation is maintained.

The age-related decline in GH secretion is initially regarded as analogous to that in adult GH deficiency (GHD) due to pituitary diseases that occur in middle-age adults or elderly persons, as both have similar patterns of bodily changes. Both GHD and ageing are associated with increased total fat mass with central abdominal fat distribution and decreased skin thickness (thinner skin), muscle mass and strength (sarcopenia), bone mass/density and exercise capacity. These ageing-related bodily changes show associations with the GH and IGF-I declines in ageing. Moreover, replacement of GH to GHD in adults restores the GH and IGF-I levels, and reverses these bodily changes. In terms of adverse effects, physiological GH replacement in GHD in adults is quite well tolerated. Hence, researchers hypothesise that replacing GH in healthy elderly persons would also achieve similar effects. However, the GH secretory response to GH-RH is still preserved in healthy ageing, while this is impaired in GHD due to pituitary diseases.

Is Growth Hormone (GH) an Anti-ageing Drug?

GH Shows Benefits on Body Composition

GH replacement improves the body composition. Replacement of recombinant human growth hormone (rhGH) to healthy elderly persons can increase circulating GH and IGF-I concentrations to the normal young adult range. Rudman et al showed that GH replacement in healthy elderly persons improved the body composition. They administered rhGH injections three times per week subcutaneously to elderly men 61-81 year old, who had low baseline serum IGF-I concentrations. The rhGH replacement increased the serum IGF-I concentrations into the youthful range. The treatment was associated with a significant 14.4% decrease in fat mass, 8.8% increase in lean body mass, and 1.6% increased in bone density in lumbar vertebrae. The skin thickness increased by 7.1% (p=0.07). Rudman et al interpreted their findings enthusiastically. They commented that the effects of 6 months of GH therapy led to improvements in lean body mass and fat mass, which were interpreted to be “equivalent in magnitude to the changes incurred during 10 to 20 years of ageing”. Because of these initial findings and the related over-interpretations, interests in the use of GH as “anti-ageing” therapy became widespread, and the off-label use of growth hormone (rhGH) as an anti-ageing drug was common, though there was insufficient evidence to support its efficacy or safety. From 1990 to 2004, there was a 10-fold increase in the number of persons using GH as an “anti-ageing” therapy. It was estimated that 20,000 to 30,000 in the US were using GH as non-indicated off-label use for this purpose. Increasing off-label use was also common in other places, including Asia.

GH has No Benefits on Muscle Strength, Physical and Cognitive Functioning

One of the hallmark of ageing is the gradual loss of muscle mass and strength, which are related to subsequent decline in physical function and the risk of falls in elderly people. GH replacement in healthy elderly persons did not improve their muscle strength.
or physical functioning, despite improvement in lean body mass. Papadakis et al showed no muscle strength improvement despite a 4.3% lean body mass increase after a 6-month therapy of GH in healthy elderly persons.\textsuperscript{17} Similar negative results were found by other studies.\textsuperscript{18-22} GH, when used together with resistance exercise, conferred no additional benefits in improving muscle strength.\textsuperscript{19} GH replacement in healthy elderly persons also did not improve their cognitive function. In a 6-month randomised controlled trial of GH versus placebo in healthy elderly persons, there was no improvement in the cognitive function.\textsuperscript{23}

**GH Replacement: Risks Outweigh Benefits in Healthy Elderly Persons**

Adverse effects are very common after GH replacement treatment in healthy elderly persons. Ankle oedema, carpal tunnel syndrome, arthralgia and gynaecomastia were commonly reported after 6-month of GH therapy.\textsuperscript{17, 24-26} Long-term risks are unknown in humans, as most clinical trials of GH were of short-duration and small sample sizes. Hence, Liu et al performed and reported a systematic review and meta-analysis of GH clinical trials in humans.\textsuperscript{27} In this meta-analysis of 31 randomised controlled studies of 220 elderly persons who had received GH (107 person-years), the mean initial daily GH dose was 14 µg per kg of body weight and the mean treatment duration was 27 weeks. In elderly persons treated with GH and compared to those not treated with GH, the overall fat mass significantly decreased and lean body mass increased. There was no change in body weight. Mild decline in the total cholesterol level was present but became non-significant after adjustment for body composition changes. There was no significant improvement in cognitive functioning, physical function, and other outcomes, including bone density and other serum lipid levels.\textsuperscript{28}

Regarding the risks of GH use, GH was reported to be relatively well tolerated in young adults with GHD,\textsuperscript{29} but not in elderly persons.\textsuperscript{30} Healthy elderly persons who were treated with GH were significantly more likely than placebo treatment to experience soft tissue oedema (50% versus 8%), arthralgia (21% versus 5%), carpal tunnel syndrome (19% versus 1%), and gynaecomastia (6% versus 0%). Other risks like diabetes mellitus and impaired fasting glucose were also more common in the GH-treated elderly persons.\textsuperscript{31}

Based on findings from experimental studies, other potential risks are possible concerns if GH replacement is given on a long-term basis as an anti-ageing therapy. The first important concern is increased cancer risks related to high normal (i.e. IGF-I levels are on the high side of the normal range) serum IGF-I levels after GH treatment. In previous epidemiological studies, high normal IGF-I levels were associated with increased risks of colon cancer,\textsuperscript{27} prostate cancer in men,\textsuperscript{28, 29} and breast cancer in women.\textsuperscript{30-33} Another concern is possible shortening of life-span (i.e. pro-ageing) rather than increased longevity (anti-ageing) with GH treatment. Currently, there are no human published data, and this concern is derived from studies in animal models. On one hand, life span was shortened in transgenic mice that over-express GH.\textsuperscript{32, 33} On the other hand, 40% to 60% increased life spans were demonstrated in GH-deficient Ames and Snell dwarf mice,\textsuperscript{34, 35} as well as in growth hormone receptor knockout mice.\textsuperscript{36, 37}

**Growth Hormone use in Special Clinical Conditions**

GH was given to critically ill adults in an attempt to improve the clinical course. However, this was found to be dangerous, as the mortality was much higher in the GH treated persons than the placebo group.\textsuperscript{38} GH was also investigated in elderly patients with hip fractures. Overall, these showed no benefits on clinical outcomes.\textsuperscript{39, 40} Stimulation of GH release from the pituitary was also investigated, using the new orally active GH-secretagogue (ghrelin mimetic MK-0677) in several studies. In a one-year randomised controlled study of healthy elderly persons, the lean body mass showed an increase but there was again no functional gain.\textsuperscript{41} The use of this GH-secretagogue (MK-0677) was also tested in a recent study involving elderly hip fracture patients. Unfortunately, despite a good increase in plasma IGF-1 levels, there was no improvement in most functional performance measures. Furthermore, the risk of congestive heart failure was increased in the MK-0677 treated group and the study was terminated prematurely, because of this unfavourable safety profile.\textsuperscript{42}

Sevigny et al also studied the use of the growth hormone secretagogue MK-0677 (ibutamoren mesylate) in Alzheimer’s disease (AD). Despite a 72.9% increase in serum IGF-I levels at 12 months, MK-0677 did not slow the rate of progression of both cognitive and activity of daily living functions in these patients with AD.\textsuperscript{43} Growth hormone was also reported to be ineffective in amyotrophic lateral sclerosis in another clinical trial.\textsuperscript{44} On the other hand, GH may be used in elderly patients with malnutrition on a short-term basis for its anabolic effects. In a randomised placebo-controlled trial, low dose and short-term use (3 weeks) of GH in elderly patients with protein-energy malnutrition (PEM) was reported to be safe, and led to a faster improvement in both the nutritional and mobility status.\textsuperscript{45} In malnourished haemodialysis patients, GH is now being tested in another clinical trial to investigate its effectiveness in this clinical population.\textsuperscript{46}

**Conclusion**

In summary, the literature published on randomised controlled trials evaluating GH therapy in healthy elders is limited but suggests that it is associated with small changes in body composition, absence of functional benefits and increased rates of adverse events. Animal studies also pointed to increased risks of cancers as well as shortening of life span with GH replacement, though there are no human data on mortality or reduced longevity after GH treatment yet. On the basis of this evidence, GH cannot be recommended as an anti-ageing therapy in healthy elderly persons. However, treatment of adult GH deficiency secondary to pituitary diseases in adults is a separate consideration. In elderly patients PEM without contraindications to GH, limited low dose and short-term use of GH is relatively safe and beneficial in speeding up the nutritional and functional recovery.
References


