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Review

Growth hormone treatment in human ageing: benefits and risks

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ABSTRACT

This paper will focus on the rationale of using Growth Hormone (GH) as an anti-ageing therapy in the healthy elderly with age-related decline in the activity of the GH/IGF-I axis, the so called "somatopause". Although the age-related decline in the activity of the GH/IGF-I axis is considered to contribute to age-related changes similar to those observed in Growth Hormone Deficient (GHD) adults, GH/IGF-I deficiency or resistance is also known to result in prolonged life expectancy, at least in animals. These data raise the question whether or not GH deficiency constitutes a beneficial adaptation to ageing and therefore requires no therapy. Moreover, although GH therapy has been shown to exert positive effects in GHD patients, its safety, efficacy and role in healthy elderly individuals is highly controversial. This review provides a comprehensive account of the implications of GH therapy in the ageing subject.

Key words: Ageing, GHRH, GHS, IGF-I, rhGH

INTRODUCTION

The age-related decline in the activity of the GH/IGF-I axis represents the most impressive example of decreased activity in the neural control of somatotroph cells as an expression of age-related changes.[1-4] Both in animals and in humans, Growth Hormone (GH) secretion undergoes clear age-related variations that are generally mirrored by IGF-I levels, the best marker of GH status, a notable exception being the neonatal period.[1-4] Spontaneous pulsatile GH secretion is high in newborns, decreases in childhood and maintains constant levels up to the onset of puberty;[5,6] later in life, a further progressive fall in 24 h GH secretory rates occurs with advancing age.[3,7,8] IGF-I levels are low at birth despite GH hypersecretion, then, from childhood to ageing, at least in well nourished subjects, IGF-I levels generally reflect the GH status, showing an increase at puberty and progressive decline from puberty to ageing;[3,4] in fact, in elderly subjects, IGF-I levels often overlap with those recorded in adult patients with severe GH deficiency (GHD).[3,4,9]

Although mechanisms underlying the age-related variations of GH release include peripheral influences (i.e. gonadal steroids, adiposity), changes in hypothalamic neuropeptides and neurotransmitters leading to decreased Growth Hormone Releasing Hormone (GHRH) secretion, as well as absolute or relative somatostatin (SS) hypersecretion seem to be

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of primary importance.[1-5] Additionally, age-related variations in ghrelin —a gastric hormone identified as a natural GH Secretagogue (GHS)- could play a role in the decreased GH secretion associated with ageing.[10-12]

It is well known that ageing is associated with changes in body composition, metabolism and structure functions[1-4] similar to those observed in adults with GHD.[9,13] These observations, together with the demonstration of an age-related decline in the activity of the GH/IGF-I axis, have led to the introduction of the neologism "somatopause": it indicates the potential link between the age-related decline in GH and IGF-I levels and frailty in ageing. It was thus hypothesized that, by restoring GH and IGF-I levels to those encountered in young people, it would be possible to counteract the age-related changes in body composition and metabolism, as it has been observed in young GHD patients receiving rhGH replacement therapy.[9,14]

Moreover, GH and IGF-I also exert remarkable effects on the central nervous system (CNS), mainly on brain plasticity and functions; changes in GH/IGF-I activity have been shown to be associated with cognitive and sleep disorders.[15-20] It was therefore hypothesized that restoration of GH and/or IGF-I levels would positively affect CNS functions frequently impaired in aged people.

This paper is focused on the controversies surrounding the use of recombinant human Growth Hormone (rhGH) and/or GH-releasing molecules aiming at "rejuvenating" the GH/IGF-I axis in the elderly, taking concurrently into account the evidence that deficiency in the GH/IGF-I axis has been associated with prolonged life, at least in animals.

EFFECTS OF rhGH THERAPY IN THE ELDERLY (Table 1)

The strong clinical similarity between adult GHD and normal ageing, together with the evidence that patients with severe GHD benefit from rhGH replacement and that elderly subjects present decreased activity of the GH/IGF-I axis, have raised the question as to whether or not aged people could benefit by a restoration of the GH and IGF-I levels to those encountered in young people. Several clinical trials focusing on the effects of rhGH replacement therapy were initiated aiming at "rejuvenating" the GH/IGF-I axis and thus acting as an anabolic anti-ageing agent.

The pioneering work of Rudman and colleagues[14]

Table 1. Main human clinical studies with rhGH treatment in healthy elderly subjects

Study	Initial daily GH dose (μg/kg/day)	Duration of treatment (months)	Positive effects	Adverse effects
Rudman 1990[14]	12.9	6	increase lean mass increase BMD	hypertension hyperglycemia
Holloway 1994[22]	43	6	decrease fat mass increase lean mass	edema carpal tunnel syndrome
Papadakis 1996[23]	12.9	6	decrease fat mass increase lean mass	edema arthralgias
Johannson 1997[24]	9.5	9	decrease fat mass improve insulin sensitivity decrease cholesterol	edema carpal tunnel syndrome arthralgias
Lange 2002[26]	12.9 (±exercise)	3	decrease fat mass increase lean mass	edema carpal tunnel syndrome
Franco 2005[25]	7.8	12	decrease fat mass improve insulin sensitivity, decrease cholesterol	edema hyperglycemia

provided the first evidence that GH treatment (30 μg/kg three times weekly for six months) in the elderly could reverse some of the changes which characterize somatopause, as for example improvement in body composition and Bone Mineral Density (BMD). In the subsequent years, further studies in aged subjects without pituitary disease have been performed, yielding controversial results.[21]

Basically, GH treatment was found to improve some parameters of body composition in healthy elderly, including an increase in lean body and muscle mass and a reduction of total body fat.[14,21,22-25] It must be noted, however, that some of the increase in lean body mass could be due to fluid retention, since methods evaluating lean body mass barely differentiate lean solid tissue from fluid mass.[9] Although GH treatment decreased total cholesterol levels, no significant effects on LDL, HDL cholesterol or triglycerides were reported.[21,22] No positive effects on other clinically important outcomes, such as muscle strength, bone mass, functional capacity and glucose metabolism, have ever been clearly demonstrated by such intervention.[14,21,23,26]

In the few studies designed to evaluate the independent effects of GH treatment and lifestyle interventions (e.g. exercise program and resistance training), no significant differences were found in body composition outcomes between subjects treated with GH plus lifestyle intervention and those treated with GH alone.[21,26,27] Furthermore, these studies could not demonstrate any additional effects of GH on strength training in terms of increased muscle strength, resistance or physical performance.[21,26,27]

It has been suggested, however, that the increase of GH/IGF-I activity might have a positive influence on ageing "frailty". In fact, some studies have demonstrated that pharmacological doses of GH were able to counteract the negative effects of acute diseases or surgery, allowing earlier return to independent life.[28] Moreover, another, potentially valuable, setting for the use of GH treatment is in elderly patients undergoing hemodialysis, where GH was able to improve important variables, such as serum albumin, total body fat-free mass and cross-sectional calf muscle area.[29]

Besides the effects on body composition and metabolism, GH and IGF-I have recently been shown to exert actions on the central nervous system (CNS), improving sleep, cognitive functions and neuronal cell survival,[15-20] in agreement with evidence that GH and IGF-I receptors are expressed in many brain areas.[20,30] Both GH and IGF-I play a role in the development and differentiation of CNS, by exerting neurotrophic, neuroprotective and metabolic effects.[20,31] These actions represent the rational basis for considering the potential usefulness of increasing GH/IGF-I levels in the ageing brain as well as in neurodegenerative disorders.

A link between the decline in somatotroph activity and cognitive function during normal ageing has not yet been proven and thus remains controversial. Some studies reported a positive correlation between total IGF-I levels or IGF/IGFBP3 ratio and cognitive function in elderly individuals,[32,33] but these results have not been confirmed by other studies.[34-36] Interestingly, IGF-1 but not GH levels correlate with cognitive parameters in elderly subjects.[17] Hence, at present there is no clear evidence that treatment with rhGH or rhIGF-I significantly improves cognitive parameters, memory or mood in normal elderly subjects.[21,37,38] These results are in contrast to those in young adult GHD patients, in whom a positive effect of GH replacement therapy on cognitive function and well-being have been reported.[9,38]

SIDE EFFECTS AND RISKS OF rhGH REPLACEMENT IN THE ELDERLY

The theoretical side effects of GH therapy in the elderly are similar to those in young GHD adults. However, concerns have been voiced about the use of GH in the elderly for many reasons. Quite early it was shown that GH administration in healthy elderly individuals very frequently caused acute adverse effects, such as fluid retention, carpal tunnel syndrome and gynecomastia.[14,21] They were generally dose-dependent, probably reflecting over-dosage and/or wide inter-individual variations in GH sensitivity.[14,21,38] Soft tissue edema was a particularly common adverse event in women treated with rhGH and, notably, it was not related to the dose used.[21] Fluid retention appears to be due to GH action on the renin-angiotensin-aldosterone axis, as demonstrated by the evidence that ACE inhibitors, as well as spironolactone, abolish the GH-induced increase in extra cellular fluid.[39]

Moreover, increased glucose and insulin concentrations, resulting from differing degrees of insulin resistance, have been recorded during rhGH therapy, in a dose-dependent manner;[21,40] this is a relevant point, considering that glycaemic control is already impaired in aged subjects.

The long-term safety of increasing GH and IGF-I levels in aged people has become a concern because of reports of an association between serum IGF-I levels and cancer risk, especially of prostate, colon and breast.[31,41-43] However, long-term data from children and adults with GHD treated with GH have shown no increased overall occurrence of *"de novo"* neoplasia or increased rate of growth of primary pituitary tumors.[44] Moreover, acromegalic patients, who have extremely high levels of both GH and IGF-I for many years, do not suffer from an increased incidence of prostate or breast cancer, though they do present an increased incidence of colonic polyps.[45,46] On the other hand, in acromegalic patients a GH-induced increase in serum IGF-I levels is accompanied by a parallel increase in serum IGFBP3 levels, which might have protective effects on tumoral cell proliferation,[31,42] unlike in normal ageing where IGFBP3 levels are generally reduced.[1]

At present, no deaths or increased cancer rates directly attributable to GH use have been reported in elderly people; this may simply reflect the short-term clinical trials so far performed or the fact that this therapy is usually given toward the end of life, not allowing enough time to affect tumor development or growth.

GH-RELEASING MOLECULES AS POTENTIAL THERAPEUTIC AGENTS IN THE ELDERLY

As the reduced function of the GH/IGF-I axis in ageing mostly reflects age-related variations in the neural control of somatotroph secretion, treatment with GH-releasing molecules has been proposed in ageing. At present, two major classes of compounds have been studied for this purpose: GHRH and GH Secreatogues (GHS).

Treatment with GHRH, generally given in short-time studies as well as in a small cohorts of patients, has been shown to restore spontaneous GH secretion and IGF-I levels in the elderly[47] and this effect could be enhanced by co-administration of arginine.[48] Some authors also reported slight but significant positive effects on body composition,[49-51] while neither increase in physical performance scores nor enhancement of the effect of exercise were demonstrated during GHRH therapy.[52] Moreover, the main problem of clinical GHRH use is that it needs to be parenterally administered.

GH-Secretagogues (GHS) are synthetic peptidyl and non-peptidyl substances endowed with strong GH-releasing effects, active after subcutaneous, intranasal and even oral administration.[53] They stimulate GH secretion by acting at the pituitary and, mainly, at the hypothalamic level on GHRH-secreting neurons.[53,54] Although GHS exert some stimulatory effect also on corticotroph secretion, this seems, however, an acute neuroendocrine effect, probably vanishing during prolonged treatment.[54]

Only a few groups have studied the clinical effects of GHS therapy in the elderly. By contrast to peptidergic GHS (e.g. GHRP-2 and Hexarelin), that showed no significant effects on either GH/ IGF-I levels or anthropometric features in elderly,[55] non-peptidergic analogues (e.g. MK-677 and L-692,429) have been demonstrated as possessing powerful GH-releasing effects, restoring IGF-I secretion in older people to levels typical of young subjects.[56,57] Long-term studies performed with the orally active GHS MK-677 resulted in a significant increase in IGF-I levels in elderly subjects coupled with increased lean body mass, but without any improvement in muscle strength.[58] Moreover, although the combination of MK-677 and alendronate improved BMD at the femoral neck, the combination provided no additional benefit compared with alendronate alone at lumbar spine, total hip or total body.[58]

Overall, although GHS restore the function of the GH/IGF-I axis in elderly humans and might be important alternatives to subcutaneously administered rhGH, there is at present no clear evidence that they significantly affect the body composition or metabolic and cognitive function associated with ageing.

GH REPLACEMENT AND LONGEVITY

Although somatopause contributes to age-related

changes in body composition, structure functions and metabolism that connote "frailty" in elderly subjects, information about the impact of GH and IGF-I axis on life expectancy is contradictory.

It has been clearly demonstrated in several animal models that reduced GH and IGF-I levels or actions are associated with significant increases in both average and maximal lifespan. In fact, GH resistant and GH-deficient mutant mice experienced substantially increased lifespan.[59] Furthermore, a significant increase in longevity has been reported in female mice that are heterozygous KO for the gene encoding the IGF-I receptor,[60] whereas transgenic mice that produce supra-physiological levels of GH for their age have markedly reduced lifespan and experience premature onset of age-related cognitive changes.[61]

Putative mechanisms linking reduced IGF-I levels with delayed ageing and prolonged longevity in animal models probably include reduced insulin release and/or enhanced insulin sensitivity.[62] However, the link between reduced GH/IGF-I activity, improvement of insulin signaling and prolonged longevity found in animal models seems to differ from human findings, which have indicated that reduced activity of the GH/IGF-I axis (normal ageing and GHD) is associated with hyperinsulinism and insulin resistance.[9,13,14] Moreover, in humans both severe GH deficiency and GH excess have been found coupled with reduced life expectancy, although these alterations could simply be the result of increased risk of cardiovascular disease, diabetes or cancer rather than the acceleration of the ageing process.[9,45,46]

In all, there is a discrepancy between the potential role of GH and/or IGF-I in life expectancy and quality of life. It should be borne in mind that, even if GH in aged subjects is proven to have no effects or a negative influence on life expectancy, the fact that it produces objective improvements in body composition, metabolism, peripheral and central functions, well-being and quality of life makes it a very reasonable clinical objective that is almost certain to be requested by most aged individuals.

CONCLUSIONS

Studies in adult GHD have shown that GH is more than simply a "growth hormone", so that it should more appropriately be renamed "somatotropic hormone". Its strong influence on body composition, metabolism and structure functions, including CNS functions, such as sleep and cognition, has amply been demonstrated by improvements in GHD patients during rhGH replacement.

Whether somatopause is simply a physiologic evolution is still a matter of debate. Although somatopause is likely to contribute to age-related clinical impairment, on the basis of available evidence, GH cannot be recommended for use by the healthy elderly, bearing in mind that GH decline with age may represent a beneficial adaptation to ageing. Conversely, the usefulness of therapy which increases GH/IGF-I levels in selected populations of "frail" elderly subjects has been suggested but not yet proven. Moreover, whenever such therapy is considered useful, the best approach would be to use molecules with a GH-releasing effect, as the pituitary GH releasable pool is fully preserved in ageing, and consequently more physiological IGF-I levels can be obtained by such intervention.

At present, no definitive answers can be provided with regard to the safety of long-term GH or GH-releasing peptide intervention in elderly individuals with the aim of reversing the effects of somatopause.

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