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Review

# Update on new therapeutic options for the somatopause

*Gian Paolo Ceda[1], Elisabetta Dall'Aglio[2], Simonetta Morganti[1], Licia Denti[1], Marcello Maggio[1], Fulvio Lauretani[3], Andrea Artoni[1], Graziano Ceresini[1], Chiara Cattabiani[1], Giorgio Valenti[1]*

[1] Section of Geriatrics, Department of Internal Medicine and Biomedical Sciences, University of Parma, Italy and Geriatric Clinic , Geriatric-Rehabilitation Department, University Hospital of Parma, Parma, Italy; [2] Section of Metabolic Diseases, Department of Internal Medicine and Biomedical Sciences, University of Parma, Italy and Metabolic Disease and Diabetology Unit, 2nd Polispecialist Medical Department, University Hospital of Parma, Parma, Italy, [3] Geriatric Unit, Geriatric-Rehabilitation Department, University Hospital of Parma, Parma, Italy

**Abstract.** During the last decade, a significant body of evidence has accumulated, indicating that the declining activity of the GH-IGF-I axis with aging might play a role in the development of frailty and in several pathological conditions commonly seen during aging, such as atherosclerosis, cardiovascular disease, and cognitive decline. GH therapy has become widely popular as antiaging therapy in order to counteract the age-related decline in muscle mass and strength and the increase in fat mass. However there are only few proven beneficial effects of GH therapy in healthy elderly subjects and its use remains highly controversial in the scientific community. In this paper we will review the current evidence related to the use of GH and/or GH-secretagogues in normal and pathological aging. (www.actabiomedica.it)

**Key words:** GH replacement therapy, IGF-1, aging, GH-secretagogues

**Abbreviations**: CHF, Chronic heart failure; HR, heart rate; IVS, interventricular septum; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVESWS, LV end-systolic wall stress; LVM, LV mass; LVPW, left ventricular posterior wall; SVR, systemic vascular resistance; ESRD, End stage renal disease; HD, hemodialysis; MHD , maintenance hemodialysis; WHR, waist to hip ratio; VAT, visceral adipose tissue; GHS, growth hormone secretagogue

## Introduction

Frailty is considered a progressive, physiologic decline of multiple body systems characterized by loss of physical function, loss of physiologic reserve and increased susceptibility to acute illness, falls, disability, institutionalization and death (1). While more prevalent in elderly patients with multiple diseases, frailty is an independent physiologic process accelerating the physiological age-related physical performance decline. In the last few years several definitions of frailty have been published and most of them are synonymous with disability, comorbidity or advanced old age (2, 3).

One of the most used definitions is that presented by Fried et al. (1) using data from the Cardiovascular Health Study. According to this definition, frailty is a clinical syndrome characterized by the presence of at least 3 out of 5 criteria, which are: unintentional weight loss , self-reported exhaustion (evaluated by modified 10 item center for epidemiological studies-depression scale (CES-D)), weakness (evaluated by grip strength), slow walking speed, and low physical activity . The presence of 1 or 2 criteria defines a condition of pre-frailty. This frailty phenotype predicts aderse outcomes such as falls, hospitalizations, disability and death , after adjusting for health status and disability at baseline, suggesting that frailty can be distinguished from disability or disease (2).

A central factor in the pathophysiology of frailty is sarcopenia, which is part of the alterations of body

composition occurring with aging. The etiology of sarcopenia include a variety of factors such as the loss of alpha-motor neurons, the reduction in dietary protein intake, a decreased level of physical activity as well as an increase in catabolic cytokines (4). A major role seems to be played by the declining levels of several anabolic hormones, and, in particular by reduced activity of the GH-IGF-1 axis. Furthermore the reduced activity of the GH-IGF-I axis now appears to be involved in many aging-related pathological conditions, such as atherosclerosis, cognitive decline and dementia. In aggregate, when these conditions are associated with inadequately low GH-IGF axis activity they are globally defined as "somatopause."

**GH replacement therapy in normal aging**

Since GH has both anabolic, by stimulating skeletal muscle protein synthesis (5) and lipolitic activities, it is not surprising that GH therapy has become widely popular as antiaging therapy in order to counteract the age-related decline in muscle mass and strength and the increase in fat mass. Indeed the rationale for using GH as an antiaging therapy is further supported by the fact that some signs and symptoms of GH deficiency (a clinical syndrome resulting from GH deficiency due to hypothalamic or pituitary defects), such as increased adiposity and decreased lean body mass, are similar to the changes occurring with aging. In this condition GH replacement therapy has been shown to exert several positive effects improving body composition , bone density, cholesterol levels and decreasing mortality (6, 7).

Despite the attention that GH therapy has received as a potential anti-aging treatment option, there are only few proven beneficial effects of GH therapy in the older population and its use remains highly controversial in the scientific community.

While Rudman et al (8) showed several years ago that a short treatment with GH was able to induce beneficial effects in healthy elderly subjects, subsequently other studies failed to confirm these old results. Nevertheless a large number of people are using GH as an antiaging therapy, even if the exact number is unknown.

The efficacy and safety of GH therapy in old subjects has been recently reviewed by Liu et al (9).

The researchers performed a systematic review and meta-analysis of randomized, controlled trials to evaluate the effects of GH on body composition, exercise capacity, bone density, serum lipid levels, and glucose metabolism. In addition, they summarized the evidence on adverse events associated with GH use in the healthy elderly. The authors included randomized, controlled trials that compared GH therapy with no GH therapy or GH and lifestyle interventions (exercise with or without diet) with lifestyle interventions alone. The length of GH treatment varied from 2 to 52 weeks with a mean of 27 weeks.

A total of 220 participants who received GH completed their respective studies; they were elderly (mean age of 69 years) and overweight (mean body mass index, 28 kg/m2). Initial daily GH dose varied with a mean of 14 μg per kg of body weight (range 1.7 - 43 μg per kg of body weight). Serum IGF-1 levels increased an average of 88% in groups receiving GH versus 2% in groups not receiving GH. GH treatment induced a decrease of fat mass (change in fat mass, -2.08 kg) and an increase of lean body mass (change in lean body mass, +2.13 kg), with no significant modification of body weight. Total cholesterol levels decreased by a mean of 11.21 mg/dl, although not significantly after adjustment for body composition changes. Other outcomes, including bone density and other serum lipid levels, did not change. Despite these beneficial effects on body composition, none of the studies showed significant effects on physical function, muscle strength or quality of life. The only study which could demonstrate a marginal beneficial effect of GH treatment on strength in the elderly was published by Blackman et al. (10), when GH was given in combination with testosterone.

Persons treated with GH were significantly more likely to experience side effects, including soft tissue edema in 50% of the GH-treated subjects, arthralgias in 21%, carpal tunnel sindrome in 19%, and gynecomastia in 5%. There was also an increase in impaired glucose regulation (22%) and new-onset diabetes (5%) in the elderly treated with GH.

From these data and the small clinical experience of GH in the healthy elderly it is not possibile to draw any

firm conclusion on its clinical relevance since the positive modifications of body composition are not accompanied by any significant functional outcome. In addition available data suggest that GH use in the healthy elderly is associated with high rates of adverse events, suggesting that risks far outweigh benefits when GH is used as an antiaging treatment in healthy older adults.

## GH therapy in pathological conditions

### *Heart failure*

The relationship between GH/IGF-I and the cardiovascular system has been demonstrated by several experimental studies. GH and IGF-I receptors are expressed in cardiac myocytes. IGF-I causes hypertrophy of cultured rat cardiomyocytes and delays cardiomyocyte apoptosis. Besides, endothelial cells have high-affinity binding sites for IGF-I and IGF-I stimulates nitric oxide (NO) production.

Alterations of the GH/IGF-I may contribute in determining cardiovascular disease as suggested by clinical studies reporting increased risk for cardiovascular morbidity and mortality both in GH deficiency (GHD) and excess (11). Epidemiological studies in the general population have also shown that IGF-I levels in the lower normal range are associated with an increased risk of ischaemic heart disease (IHD) (12, 13) and stroke (14).

Experimental studies have shown that GH or GH-releasing peptides induce beneficial effects on cardiac function, vascular resistance, and survival in animals with postischemic heart failure.

Based on these experimental observations, several clinical studies have been performed to evaluate the effects of GH given to patients with CHF in addition to conventional therapy. However, the results were conflicting and inconclusive since most studies included small numbers of patients, raising the possibility that non significant results were related in part to inadequate statistical power. To obtain a more reliable picture of the effect of GH administration in patients with CHF a recent meta-analysis was conducted (15), in which cardiovascular data obtained from 12 trials, selected from three databases, were analyzed. The results showed that GH treatment leads to an increase in LVEF and a reduction in SVR, suggesting an improvement in systemic hemodynamics. In addition, GH treatment induced long-term modifications in cardiac morphology, *i.e.* a reduction in LVEDD and an increase in left ventricular wall thickness (IVS and LVPW), resulting in reduced LVESWS. Similar results on LVEF, LVM, and exercise capacity were reported after treatment with the growth hormone-releasing factor ghrelin in patients with CHF (16).

Very recently Cittadini et al (17) investigated the prevalence of GH deficiency in a group of patients with CHF and evaluated the cardiovascular effects of GH replacement therapy.

158 patients with CHF were studied with a GH stimulation test using GHRH plus arginine; sixty-three patients satisfied the criteria for GH deficiency, and 56 of them were enrolled in a GH replacement therapy protocol using GH at a dose of 12 μg/kg every other day for 6 months.

GH replacement therapy in these patients improved exercise capacity, vascular reactivity, left ventricular function, and indices of quality of life. These data suggest that GH replacement therapy should be performed in properly selected CHF patients.

### *Chronic kidney disease*

Nutritional markers, such as lean body mass (LBM) and serum albumin, predict outcome in ESRD patients on mantenance hemodialysis, who experience high rates of morbidity and mortality and decreased quality of life. The administration of growth hormone (hGH) may improve the nutritional and cardiovascular health of these patients and consequently reduce morbidity and mortality. Indeed, in several studies, GH has been shown to reduce protein catabolism and improve nutritional status; however the number of patients studied was small and treatment was performed for short periods of time.

In a quite large study (18), 139 adult patients, who were on maintenance hemodialysis and had low albumin levels (<40 g/L), were randomly treated for 6 months with placebo or different doses of GH (20, 35, or 50 μg/kg/d of hGH). In these patients several parameters were monitored such as change in LBM and al-

bumin (primary outcomes), health-related quality of life and safety parameters. The study showed that hGH treatment significantly increased LBM at all GH doses (mean of 2.5 kg *versus* -0.4 kg for pooled hGH groups *versus* placebo), as well as serum albumin and other nutritional markers, such as serum transferrin and serum HDL, while plasma homocysteine was reduced. There was an improvement in some quality-of-life subscale parameters and no differences in clinically relevant adverse events between groups. These data seem to suggest a beneficial effect of hGH therapy in adult patients who are on maintenance hemodialysis.

However also in this condition data are scanty and the number of patients treated too small to draw definite conclusions about the utility of GH therapy.

A long-term study is warranted to investigate whether these treatment benefits result in reduced mortality and morbidity. To this end an ongoing trial, the OPPORTUNITY Trial (19), will examine whether GH will reduce mortality and morbidity and improve overall health in hypoalbuminemic HD patients. This prospective, double-blind, multicenter, randomized clinical trial will enroll 2500 MHD patients, up to 50% with diabetes mellitus, from 22 countries, randomized to receive daily injections of GH (20 microg/kg per day) or placebo for 104 weeks.

The OPPORTUNITY Trial is the first large-scale randomized clinical trial in adult MHD patients evaluating the response to GH of such clinical endpoints as mortality, morbidity, markers of body protein mass, inflammation, exercise capacity, and health related quality of life.

*Obesity*

Obesity is associated with a major increase in morbidity and mortality. The secretion of GH is decreased in obesity. Although the lipolytic and anabolic effects of GH are well established, the pathophysiological role of GH in obesity remains uncertain. The effects of human GH in obesity and its associated cardiometabolic risk factors, including body composition, lipid profile, blood pressure, and glycemia, have been examined in several studies, leading to conflicting results.

Recently a comprehensive metaanalysis (20) of clinical studies examining the efficacy and safety of rhGH therapy in patients with simple obesity was conducted. 24 studies were included in the analysis for a total number of 477 subjects who completed their study; treatment duration ranged from 3–72 wk (median, 11.5 wk).

GH therapy improved body fat distribution, leading to a decrease in WHR and visceral adiposity.

GH therapy favorably affected lipid profile, leading to a decrease in total and LDL-cholesterol. These benefits occurred regardless of concurrently recommended diet. However these effects are small and would not justify a clinically relevant role for rhGH therapy in the treatment of visceral adiposity, particularly in view of the supraphysiological rhGH doses used in many studies as well as the high cost of rhGH therapy and a clear association of rhGH therapy with arthralgias, peripheral edema, and paresthesias.

In addition, there was a small increase in fasting plasma glucose and insulinemia, that appeared to be mitigated in longer studies, perhaps reflecting improvement in visceral adiposity and insulin resistance, as it has also been suggested in adults with GHD.

In order to counteract the diabetogenic effect of GH in obese people, a trial has been recently performed with the use of GH in combination with Pioglitazone (21). In this study 62 abdominally obese subjects aged 40 to 75 years were treated for 40 weeks with GH at a dose of 8 μg/kg/d (or placebo) and pioglitazone at 30 mg/d or placebo. As expected, GH induced a decrease in visceral fat area, the addition of pioglitazione to GH attenuated the short term diabetogenic effect of GH and the drug combination reduced VAT and insulin resistance over time, suggesting that GH plus PIO my have added benefit on body composition and insulin sensitivity in the metabolic sindrome.

However, it must be emphasized that the reduction in insulin resistance and VAT induced by GH and PIO are similar to the effects induced by diet and/or exercise.

**The role of GH-secretagogues**

Ghrelin and synthetic GH secretagogues have been shown to possess several potentially beneficial effects including appetite stimulation, endothelial func-

tion improvement and inflammation inhibition, and salutary cardiovascular function.

MK-0677 is highly selective and a potent orally active GHS-R1a agonist with suitable pharmacokinetics for once daily administration in humans. This synthetic compound has been shown to possess an excellent safety profile. Previous studies on chronic treatment of elderly subjects with this compound have documented the following benefits: (a) the ability of MK 677 to restore the amplitude and frequency of episodic GH release in frail elderly subjects (68- to 94-year-old) to those typical of young adults (22); (b) to increase lean mass and to induce modest improvements in shoulder and knee strength (23) ; (c) to accelerate recovery following hip fracture in elderly subjects treated for 6 months with MK-0677 (24); to increase bone mineral density after 18 months treatment in postmenopausal women (25) and to prevent any hyperstimulation of the GH/IGF-1 axis by endogenous regulatory feedback loops.

More recently Nass and coll (26) studied the effects of one year treatment on body composition and functional outcomes in a group of healthy older adults. The ghrelin mimetic increased pulsatile growth hormone secretion to young adult levels. Over 1 year, lean fat-free mass increased 1.1 kg with MK-677 and decreased 0.5 kg with placebo. However MK-677 did not affect strength and physical function, whereas insulin sensitivity decreased and mean serum glucose levels increased. Study power (duration and participant number) was insufficient to evaluate functional end points in healthy elderly persons.

To investigate the hormonal, body composition, and physical performance effects, and safety, of the orally active GHS capromorelin, another group of Researchers studied older adults with mild functional limitations (27). For this study 395 healthy men and women aged 65 to 84 years at risk for functional decline were selected and randomized to different doses of the drug for one year. The results showed an increase of GH secretion and IGF-1 levels, an increase of LBM and body weigth, and , more importantly, an improvement in some measures of physical performance such as tandem walk and stair climb. These data suggest that admnistration of orally active GHSs can improve physical performance in frail but otherwise healthy older adults, even if further research is needed to fully appraise the risk benefit profile of GHSs and determine their potential utility for maintaining and improving physical function and reducing disability in selected populations of older adults.

Maintaining IGF-1 at young adult levels appears also to be important for cognitive function such as spatial memory and processing speed in humans. Infact the age-related decline in circulating levels of IGF-1 is associated with cognitive functions that decline with ageing (28). Therefore , not surprisingly, GH secretagogues, such as MK-677, which stimulate the release of GH and produce a robust upregulation of circulating IGF-1 levels, have been employed in people affected by Alzheimer's disease in order to verify if this treatment was able to modify or improve the course of the disease. A double-blind, multicenter study was conducted in 563 patients with mild to moderate AD , randomized to receive MK-677 25 mg or placebo daily for 12 months. Despite a robust increase of IGF-1 levels, no significant modification of cognitive performance was observed, suggesting that the age-related decline of the somatotropic axis is not a major contributor to the pathways underlying AD or its clinical manifestations.

In conclusion, as Morley wrote "…any hope of a fountain of youth to stop people from getting older is a long way off, with science just beginning to understand the complex genetic, physical and hormonal causes of aging. An essential, but still unanswered question, is whether the decrease in hormone levels seen with aging is physiological, conveying a benefit, or pathological, causing harm" (30).

Further longitudinal studies are required to determine the risk and benefit of GH replacement in healthy older persons and to identify whether individuals can benefit from the anabolic effects of GH or GH-secretagogues.

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Correspondence: Gian Paolo Ceda, MD
University of Parma,
Department of Internal Medicine and Biomedical Sciences,
Section of Geriatrics, School of Geriatrics
Via Gramsci 14, 43100 Parma, Italy
Tel. 0039-0521-703307,
Fax 0039 0521-237761
E-mail: gpceda@unipr.it