Statement by the Growth Hormone Research Society on the GH/IGF-I Axis in Extending Health Span

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Despite the fact that growth hormone (GH) has not been approved for antiaging purposes, its use for this indication is widespread and increasing. The Growth Hormone Research Society (GRS) convened an international workshop to critically review and debate the available evidence related to the use of GH in the older adults and the relationship between the GH/insulin-like growth factor I (IGF-I) axis and the aging process. This statement presents the conclusions reached and gives recommendations for future studies in this research field regarding the use of GH and growth hormone secretagogues (GHS) for promoting health span. The participants concluded that, until future clinical research in this area is conducted, in particular carefully designed, long-term studies, using validated outcome parameters, the clinical use of GH or GHS in older adults, alone or in combination with testosterone, cannot be recommended. In addition, future basic studies in model systems, to continue to unravel GH/IGF-I effects related to human life span and health span, were advocated.

Background to the Workshop Plan and Process

Abuse of growth hormone (GH) for antiaging purposes is widespread and continues to increase, despite the fact that neither the U.S. Food and Drug Administration nor the European Medicines Agency has approved the use of GH for this indication (1). Simultaneously, clinical research is ongoing and studies are being published that further evaluate the potential usefulness of increasing secretion of GH in older adults. Likewise, extensive research is being conducted in various animal models to elucidate the association between the activity of the GH/IGF-I axis and health span.

The Growth Hormone Research Society (GRS) convened an international workshop on May 28–31, 2008, in Reykjavik, Iceland, to critically review and debate the available evidence related to the use of GH in older adults and the relationship between the GH/IGF-I axis and the aging process, as well as life span and health span, and possible intervention strategies. Prior to the meeting, two critical reviews of the animal and human studies were prepared and circulated to the participants (2,3). Leading experts in both basic and clinical sciences were then invited to participate in the creation of a written statement based on the available published evidence. Representatives of industry supporters of the GRS participated in all discussions leading to the development of the statement but did not participate in either the writing of or voting on the statements. The workshop participants identified and addressed key issues employing a previously defined model used to achieve consensus statements (4,5). The resulting statement gives recommendations for future studies in this research field regarding the use of GH and growth hormone secretagogues (GHS) for promoting health span (defined as the period of life characterized by freedom from disability and disease and the ability to enjoy an independent life without functional limitations).

The review, discussion, and analysis of the available literature focused on two approaches to the GH/IGF-I and aging research field and the study of health span:

1. Animal studies: In animal models of aging, mutations in genes of the GH/IGF-I axis have been implicated in extended longevity. In addition, studies have characterized the molecular, cellular, and integrative biological mechanisms and determinants of prolongation of life span.

2. Human studies: In response to the documented beneficial effects of GH replacement in growth hormone–deficient (GHD) patients, studies have used GH in an attempt to increase health span in the “normal” healthy aging population.

In addition to these two approaches, the participants in the workshop also reviewed the available information on surrogate markers for physiological aging and the use of appropriate outcome parameters, both of which are essential for interventional studies in the aging human. Attention was also given to documented and potential adverse events and safety issues.

Demographic Data

The worldwide increase in the aging population is having and will continue to have a significant impact on society and the health system in the coming decades. By 2025, the global population of people aged 65 years and older will exceed 800 million, two thirds of whom will live in developing countries. As a result of this age shift in the population, emerging major health care goals are the prevention and postponement of disease and disability and the maintenance of health, independence, and functional status of the aging population. These goals can be defined as increasing the health span of older adults.
**ANIMAL MODELS WITH EXTENDED LIFE SPAN**

The review by Berryman and colleagues (2) provided the participants with a detailed description of studies in animal models with extended life span.

**Evidence that Decreases in GH/IGF-I Action Prolongs Longevity and Increases Health Span**

Studies in multiple experimental organisms, ranging from nematodes to mice, have provided substantial evidence that reduction in the activity of the GH/IGF-I axis is associated with increased longevity. The increase in life span in these experimental models is associated with decreased neoplastic disease (6,7) and improved metabolic control (8), including reduced cardiovascular disease (9) and improved resistance to various stressors (10–12). The role of insulin sensitivity in prolonging life span is controversial as some of the long-lived animals are insulin sensitive (8,13), whereas others are insulin resistant (14,15).

**Effects of Caloric Restriction in Prolongation of Life Span in Animals**

Caloric restriction (CR) is an established intervention that prolongs life span in a variety of species and is associated with reduced serum IGF-I concentrations (16). Chronic CR (“undernutrition without malnutrition”), when started well before old age, extends life span in most, although not all, laboratory animal models in which it has been tested. Although the mechanism(s) of its effects are not understood, the fact that a single intervention slows multiple age-related changes, including lowering cancer incidence (17), makes this an important starting point for further investigations.

The workshop participants agreed that the implications of CR for humans are currently unclear and that potential negative effects on muscle mass, bone mass, aerobic capacity, and reproductive and immune functions are important considerations. Furthermore, the practicality of restricting calories for long periods of time in humans was questioned. The results of ongoing long-term human CR studies, such as the CALERIE study (18), are awaited.

**Controversies and Limitations of In Vitro and Animal Models with Genetic Manipulation of the GH/IGF-I Axis**

Altering the GH/IGF-I axis does not always result in beneficial effects: examples include (a) the conditional disruption of IGF-I production in mouse liver, which resulted in mice with an 80% decrease in serum IGF-I (19) and a shortened life span; (b) the global IGF-I gene knockout mouse, which showed a greater than 80% mortality before age 6 months (20); and (c) IGF-I receptor gene deletion in mouse muscle, which resulted in animals that developed diabetes mellitus and had a significantly shortened life span. Data in nematodes and fruit flies indicate that reductions in insulin/IGF-I homologous signaling are sufficient to extend life span and health span only when introduced in the adult organism (21).

GH has been administered to mice and rats over their life span in several pharmacological doses for risk assessment of carcinogenic potential. Importantly, daily subcutaneous injections of recombinant mouse GH were well tolerated and had no effects on survival, longevity, or incidence of tumors (22). Overall, it should also be remembered that there are always limitations to attempts to apply observations from genetically homogeneous animals bred and maintained under laboratory conditions. In particular, single gene mutations tend to oversimplify what are frequently multimodal disorders.

Despite these controversies, these animal models provide important clues about possible pathways affecting longevity and could help in the identification of new molecular targets or agents that may modulate human life span. These animal studies have led to the conclusion that reduced activity of the GH/IGF-I axis is associated with increased longevity. This has also been supported by some human epidemiological studies, including recent studies in centenarians (23). However, environmental conditions and other factors that significantly affect life span in humans independent of the GH/IGF-I axis must be considered.

**HUMAN STUDIES TO EXTEND HEALTH SPAN**

The review by Nass and colleagues (3) provided the participants with a detailed description of studies that have attempted to extend health span in humans.

**Distinction Between Physiological and Pathophysiological Aging**

The decline in health and function with aging is a multi-component complex. Key features of the aging process include unintentional weight loss; loss of mass, structure, and function of muscle and bone; and cognitive impairment leading ultimately to loss of independence. Although it is difficult, if not impossible, to clearly distinguish physiological from pathophysiological aging, frailty is one of the central features of the aging process and possibly represents an independent process.

**Frailty as One of the Central Features of Aging**

An important objective of the workshop was to identify lifestyle or pharmaceutical interventions with the potential to either prevent or reverse frailty. The frailty phenotype definition used by the Cardiovascular Health Study was adopted by the workshop (24). This definition has predictive value for adverse outcomes such as susceptibility to acute illness, disability, falls, hospitalization, and death. The frailty definition requires the presence of three or more of the five criteria listed in Table 1.
Selection of successful drugs for preventing or retarding the development of frailty will depend on identification of fundamental processes that lead to frailty, for example, molecules identified from animal and longitudinal human studies. Potential candidates include nonsteroidal anabolics, insulin sensitizers, anti-inflammatory drugs, orexigenic agents, and cardiovascular risk modifiers. The workshop focused on the GH/IGF-I axis; and therefore, only interventions within this area were discussed.

Sarcopenia and Frailty

One of the hallmarks of aging is the loss of muscle mass, that is, sarcopenia, which is part of a frailty syndrome, and is predictive of falls, hospitalizations, disability, and death in the elderly. The prevalence of sarcopenia increases with age, and the reported muscle loss ranges from 1 to 5% per decade, after the age of 40 years (25).

The mechanism(s) of muscle mass decline may be intrinsic to muscle and/or susceptible to influence by extrinsic factors acting on muscle, such as changes in muscle innervation, nutrition, hormones, and/or exercise. No direct causal relationship has been established between sarcopenia, frailty, and health span. However, the links between age-dependent muscle loss and physical frailty and decreased capacity of independent living are well established.

Clinical trials using selected novel agents to target muscle mass and function are currently underway (e.g., with selective androgen receptor modulators, ghrelin agonists, and antimyostatin antibodies). It will be important to know whether these improve muscle function as the quality of increased muscle mass is important in this population. However, the mechanisms underlying improved muscle mass and function are complex and not limited to direct effects on muscle (3).

This opens up the possibility of a broader range of targets for therapeutic intervention, for example, central nervous system and motor neuron function. Although it is likely premature to define a population of participants with sarcopenia of aging for an interventional study targeting the GH/IGF-I axis, frail participants with low serum GH and IGF-I were considered to be potential candidates.

Interventions to Avert or Reverse Frailty by GH/GHS Therapy

The endogenous levels of GH (also called somatotropin) decline as a function of age, a physiological phenomenon for which the term “somatopause” has been coined. This age-related decline in GH is also associated with a concomitant increase in fat mass (adiposity) and a decrease of lean body mass (26).

Clinical trials of short-term administration of GH in healthy older adults have demonstrated that GH can reverse some aspects of age-related changes in body composition, including increasing lean body mass (27). However, none of the studies reported in older adults have shown a beneficial effect of GH administration on muscle strength or physical or quality-of-life parameters. In addition, data on long-term efficacy and safety of such treatment are lacking. Nonetheless, worldwide, the “off label” use of recombinant human GH as an antiaging therapy has increased rapidly.

Ghrelin, a 28-amino acid peptide that is mainly released from the stomach, induces several effects that could be potentially beneficial for the older population. Besides increasing the levels of GH and IGF-I, it exerts orexigenic effects (28). Orally active ghrelin mimetics or GHS’s are also available that have potential beneficial effects in catabolic conditions, increasing appetite and fat-free mass in healthy older adults after 1 year of treatment (29). Because ghrelin and its mimetics also act by other non-GH mechanisms, such as by affecting the thymus and proinflammatory cytokine pathways (30), it has been suggested that the effects of an GHS should be investigated on multiple target tissues in addition to muscle, fat, and bone, such as the heart, brain, and immune system (31).

Exercise

Although decreased function of the GH/IGF-I axis is linked to sarcopenia, the concept that resistance exercise alone can ameliorate the impact of sarcopenia has been supported by data from both humans and animals (32). No additional effect of GH on muscle mass has been observed (33). These results therefore favor the use of exercise versus GH as an intervention to prevent sarcopenia in older adults.

Combination Therapy

Administration of testosterone in combination with GH in older men has been studied due to the concomitant decline of testosterone and GH with aging. However, controlled trials testing the combined effects of both agents, while showing an improvement in lean body mass, showed no substantial improvement in muscle function (34). No studies in which ghrelin mimetics have been used in combination with testosterone have been reported thus far. Therefore, based on our current knowledge, combined use of testosterone with either GH and GH-releasing hormone or GHS cannot be recommended for treatment of age-related sarcopenia.
Safety of GH/GHS Therapy in the Elderly

GH replacement therapy in severely GHD adult patients with pituitary–hypothalamic disease has proven to be efficacious and safe (4). However, these results cannot be extrapolated to the use of GH in older adults, who exhibit increased inherent risk of diabetes mellitus and de novo neoplasia (27). The available data published in the literature show dose–dependent diabetogenic effects in short-term GH studies in older adults (27).

Principal Difficulties in Designing Intervention Studies to Extend Health Span in the Elderly

If healthy functional muscle mass can be maintained in the elderly, it is likely to result in major beneficial outcomes of independent living. The focus of intervention should be both preventative and therapeutic, and further studies on outcome or function are therefore needed.

Two different strategies were suggested to obtain proof of concept for the use of GH/GHS in the elderly:

1. Improvement or prevention of decline in functional outcome parameters (for suggested primary and secondary outcome parameters see Table 2).
2. Increased survival.

The selection of study participants should not be based on age alone because of the heterogeneity in the older population. Instead, selection should probably include a central feature of aging, such as muscle loss or weight loss, in combination with a serum marker for the GH/IGF-I status. In addition, the study design needs to incorporate placebo control(s) to be able to show prevention of decline.

Based on the available data on strength and function, future studies should be long term with a duration ranging of at least 1 year and ideally up to 5 years. Finally, the timing of the intervention (age range) is most likely of importance for the experimental outcome. No data are currently available to justify a recommendation. It is likely that initial studies will concentrate on a prefrail older population and later studies will include younger individuals (Table 2).

CONCLUSION

Two salient realities became manifest during the workshop: (1) Animal studies suggest that a reduction of the GH/IGF-I axis extends life span and (2) human studies suggest that enhancing the activity of the GH/IGF-I axis in the elderly may extend health span. The awareness of the paradox between the animal studies and the human hypothesis should be at the forefront when future trials in humans are planned. We know that it is possible to enhance GH production in older adults, and we also know that by doing so we can make favorable changes to body composition. However, properly designed studies need to be conducted to elucidate clinically relevant efficacy (functional activity, quality of life, and life expectancy), long-term safety, and pharmacoeconomic issues.

SUMMARY OF GRS recommendations for GH/GHS use in the elderly

Further Basic Science Studies Regarding Extending Life Span and Health Span

We recommend future basic studies in nonhuman model systems to continue to unravel GH/IGF-I effects related to human life span and health span. These should include elucidation of the intracellular signaling systems that are induced by the GH/IGF-I axis. Also, experiments designed to generate tissue- and temporal-specific alterations of the GH/IGF-I axis, to determine their effects on aging, are recommended.

Design of Future Studies to Investigate Enhancement of Health Span

Given the expected demographic age shift in the world population, future clinical research in this area, with carefully designed, long-term studies, using validated outcome parameters, is strongly recommended. Until the results of such studies are available, the clinical use of GH or GHS in older adults, alone or in combination with testosterone, cannot be recommended.

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References


Table 2. Suggested Outcome Measures for Prospective Placebo Controlled Clinical Trial of Growth Hormone or Growth Hormone Secretagogues

<table>
<thead>
<tr>
<th>Primary outcome measures</th>
<th>Secondary outcome measures</th>
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<tbody>
<tr>
<td>Gait speed</td>
<td>Mortality</td>
</tr>
<tr>
<td>Short Physical Performance Battery</td>
<td>Hospitalizations or institutionalizations</td>
</tr>
<tr>
<td>6-min walk</td>
<td>Cognitive function</td>
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<tr>
<td>400-m walk</td>
<td>Loss of independence</td>
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