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Mini-Review

Human Growth Hormone Therapy -

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ABSTRACT

In this mini-review benefits and risks of Growth Hormone (GH) replacement therapy in adults with GH deficiency are discussed. In addition, a cost-benefit analysis will be made and the inevitable illicit use and doping of growth hormone will be considered. Global human growth hormone market is expected to rise to USD 7,1 billion in 2025 and is the fastest growing market segment in Pharma due to extending GH treatment indications and investments of large players. Growth hormone use in anti-aging is highly controversial but booming. New guidelines are discussed as well as the recently FDA approved ghrelin oral GH stimulation test. The very recent horizon view of the Growth Hormone Research Society is discussed as well as the proteomic search for putative new biomarkers for detecting GH deficiency in patients and doping in athletes. GH replacement therapy in children remains a costly treatment with USD 35.000-50.000 for each gained inch in height.

INTRODUCTION

Growth Hormone Deficiency (GHD) in adulthood is characterized by alterations in body composition, decreased capacity for exercise and Quality of Life (QOL), as well as a series of unfavourable changes in cardiovascular function, lipid and carbohydrate metabolism [1,2]. The diagnosis is based on the combination of pituitary disease, hypopituitarism and a decrease in the concentration of Insulin-Like Growth Factor (IGF-1) or in diminished GH responses to different stimuli [3-5].

Replacement therapy with recombinant GH has been available since the 1980's. The experience accumulated since then is extensive. However, the use of hGH is no longer restricted to children and adolescents with GH deficiency or Idiopathic Short Stature (ISS) or primary Insulin-Like Growth Factor-1 (IGF-1) deficiency.

Rising cases of pituitary dysfunction and increasing use of hGH are likely to drive the global human growth hormone market. This is expected to reach USD 7,1 billion by 2025. The growth hormone deficiency segment accounted for the highest share of the market in 2016 and is estimated to observe the fastest growth of the market. This can be attributed to increasing incidence of pituitary dysfunctioning and investment by major players for the research and development of human growth hormone drugs.

Turner syndrome, growth hormone deficiency, Prader-Willi syndrome, ISS and small for Gestational Age (SGA) are major disorders in which Growth Hormone (GH) are used. Additionally, growth hormone also received an approval for other indications such as chronic kidney disease, SHX gene haploinsufficiency and Noonan syndrome. Although the FDA has not approved the use of hGH as anti-aging therapy many practitioners offer injections of growth hormones at higher prices. The hGH therapy is aggressively promoted for advanced age symptoms [6,7].

Fusion of biochemistry, biology and nanotechnologies will result in new challenges as hybrid, microfluidic delivery systems.

In this mini-review benefits and risks of GH replacement therapy in adults with GH deficiency are discussed. In addition, a cost-benefit analysis will be made and the inevitable illicit use and doping of growth hormone will be considered.

BENEFITS OF TREATMENT WITH GROWTH HORMONE (HGH):

GH replacement therapy is associated with beneficial effects on body composition, bone structure, health-related QOL and several cardiovascular risk factors [8-10].

Body composition

Initial studies showed that treatment with GH induced a decrease

in fat mass and an increase in lean mass [11]. In a cohort of 156 patients with GHD Elbornsson et.al., [12] reported an improvement in lean body mass maintained for 15 years and a marked initial decrease in fat mass. This was followed by a slowly progressive increase over time in possible relation with the aging process. A recent systematic review concluded that the long-term effects on Body Mass Index (BMI) appear to be inconclusive, with some studies reporting an increase and other reporting no change [10]. Most long-term studies report no effect of GH replacement therapy on waist-hip ratio or waist circumference. A slight but significant increase in waist circumference has been reported in one study [13]. It has been postulated that the observed increase in body mass index and waist circumference in some studies is in line with the normal aging process [14,15].

Data from a study by Filipsson Nyström et.al., showed that discontinuation of GH therapy was followed by an increase in abdominal subcutaneous and visceral fat and a decrease in thigh muscle mass [16]. A recent meta-analysis of 22 trials including 591 GH-and 562 placebo-treated patients found that mean lean body mass was increased by 2,6 kg in GH-treated subjects versus 0,04 kg in the placebo group. Fat mass was reduced by 2,19 kg versus 0,31 kg (GH vs placebo). Changes in lean body mass and fat mass were dose-related with high doses being more effective than low doses [17].

Lean body mass, including both skeletal muscle mass and tissue hydration is increased with GH replacement [18]. The lean body mass data may not be accurate as GH replacement is associated with an increase in the intracellular water component. This is caused by increased distal tubular sodium reabsorption, an increase in plasma renin activity and decreased brain natriuretic peptide levels [19,10].

In a study by Gotherstrom et.al., [20] 10 years of GH treatment in patients with GHD resulted in increased muscle strength during the first half of the study and protection from the decline from aging later. These data, although indirectly, clearly suggest a real increase in muscle mass.

Bone structure

Replacement therapy with GH in adults with GHD increases Bone Mineral Density (BMD) and helps to optimize peak bone density in patients who have persistent GH deficiency during the transition from adolescence to adulthood [9,10,21]. The effect on BMD is greater at vertebral than femoral level and after 18-24 months of treatment most studies show an increase of 4-10% of BMD [22]. In patients with childhood-onset GHD it has been shown that the continuation or reinstatement of treatment for two years, in patients who completed growth, induced a significant increase in BMD compared to untreated patients [23]. Therefore, the continuation of GH treatment during the period of transition from childhood to adulthood is recommended to obtain complete bone maturation.

A prospective study in 18 patients with GHD showed that seven years of GH treatment induced an increase in lumbar spine BMD which stabilizes during long-term therapy. However, a significant positive effect on bone microarchitecture could not be demonstrated in these patients [24]. Two recent meta-analyses have suggested that the beneficial effect of GH therapy on BMD in adults with GHD is mainly affected by gender, age, dose and treatment duration [25,26].

In a cohort of 230 adult GHD patients followed up to 15 years Appelman-Dijkstra et.al., [27] demonstrated a sustained increase in BMD at the lumbar spine, particularly in men and stabilization of BMD values at the femoral neck. This study suggested that the clinical fractures incidence was not increased during long-term GH replacement therapy.

Estrogenic hormonal status exerts also influence on the GH replacement therapy effects on bone metabolism. In a prospective, single-center study, including 87 consecutive patients (52 men and 35 women) with adult-onset GHD a sustained increase in total, lumbar, femoral neck BMD and bone mineral content was induced during GH replacement therapy. There was a tendency for women on estrogen treatment to have a greater increase in bone mass and bone density compared with women without estrogen replacement. This study suggests that adequate estrogen replacement is needed in order to have an optimal response in bone mineral density in GHD women [28].

Quality of Life (QOL)

GH treatment improves health-related QOL in the majority of patients. Most of the improvement in QOL occurs during the first year of treatment, although this effect persists in the medium and long term [29]. Sustained improvement in QOL scores has been shown to be more marked in women and in patients with low QOL at baseline [30,31].

Cardiovascular risk factors

Treatment with GH in patients with GHD improves several cardiovascular risk factors, such as lipid profile, endothelial and cardiovascular markers [32,33]. Dyslipidemia has been considered the strongest contributor of the excess in cardiovascular risk associated with hypopituitarism [33]. Most studies have shown an increase in High-Density Lipoprotein (HDL) cholesterol and a decrease in total cholesterol and Low-Density Lipoprotein (LDL) cholesterol after administration of GH [34]. Withdrawal of GH treatment for four months after more than three years of administration was accompanied by an increase in total and LDL-cholesterol [16]. The positive effect of GH on lipid profile has been confirmed in a long-term 15 year-prospective study. Furthermore, a slight decrease in diastolic blood pressure has been demonstrated in a meta-analysis of placebo-controlled studies [35]. The relationship between GHD and atherosclerosis is not always straightforward as Oliveira et.al., showed in a model of congenital GH deficiency [36,37]. In this model, atherosclerosis was accelerated instead of improving by a GH depot administration for six months.

Inflammatory markers are elevated in patients with GHD and treatment with GH can improve low-grade inflammation, as documented by a reduction in C-reactive protein, TNF-alpha and interleukin-6 [16,33,36]. Increased thickness of the carotid intima-media is an important predictor of coronary disease in epidemiological studies. Replacement with GH in patients with GHD has been shown to decrease that parameter [37]. In patients

with obesity and decreased GH secretion, randomized and placebo-controlled administration of a GHRH analogue induced a decrease in visceral fat mass and in the intima-media thickness of the carotid, in addition to a moderate elevation of IGF-1 [38].

Growth hormone replacement has a positive effect on left ventricular mass, interventricular septal and left ventricular posterior wall thickness, left ventricular ejection diastolic diameters and stroke volume, *via* echocardiographic evaluations in adults with GHD. It improves both exercise capacity and cardiac function [39]. These patients demonstrated increased oxygen uptake and power output with cycle ergometry with increased skeletal muscle mass and aerobic capacity.

Side effects and risks

The most common side effects of GH treatment in GHD adults result from fluid retention, with peripheral edema, arthralgias, carpal tunnel syndrome, paresthesias and worsening of glucose tolerance. These hormonal side effects generally respond to dose reduction. Older and more obese patients are more susceptible to side effects of GH treatment. In studies using higher than recommended doses of GH more frequent adverse outcomes have been observed [19,34].

Benign intracranial hypertension (pseudotumor cerebri) has been linked to GH treatment in children but is rare in adults [40]. An increased optic disc can be found in congenital GH deficiency and may not necessarily be linked to GH therapy or pseudotumor cerebri [41]. Another rare but reported complication of GH therapy is macular edema in non-diabetic patients [41]. Early clinical trials reported insulin resistance and diabetes mellitus in patients receiving GHRT. These small initial studies reported impaired fasting glucose and insulin levels within the first year of GH therapy [42-44].

There is no evidence that GH replacement in adults increases the risk of de novo or recurrent malignancy. For survivors of childhood cancer GH treatment may further slightly increase the already increased risk of developing a second neoplasm although this increase was not seen in the large childhood cancer survival study [45]. However, there are no comparable data for adult GHRT. Most of the concerns about increased cancer rates in GHD patients treated with GH have primarily focused on observational data on survivors of childhood leukemia, in whom cranial irradiation frequently leads to GHD. These reports may be misleading since it is not clear if tumor development noted reflected a new or recurrent malignancy, or due to irradiation or other past treatment of existing tumors [46].

Growth hormone is a mitogen however and despite several studies that show no demonstrated risk of malignancy with GHRT the use of GH is contraindicated in active malignancy out of concern it might accelerate the growth of an existing neoplasm. GH-therapy should be stopped in all patients with active malignancy until the underlying condition is controlled [46,47].

GROWTH HORMONE IN ATHLETICS

Anecdotal evidence suggests that GH and IGF-1 are frequently abused by athletes for their anabolic and lipolytic properties. GH has been touted to achieve faster recovery from injury and enhance ergogenicity, although there is no evidence that GH or IGF-1 actually improves competitive performance in young healthy adults [48-52]. Conducting randomized controlled clinical trials is challenging, due to frequent concomitant use of insulin and anabolic steroids. GH and IGF-1 appear on many lists of prohibited substances in competition

and their use is banned by the World Anti-Doping Agency (WADA). As noted in the U.S., administration of GH (but not IGF-1, GHRH or ghrelin mimetic GH secretagogues) to enhance athletic performance is legally prohibited. It is rarely prosecuted. Legal proceedings have generally been based on false testimony about its use rather than the use itself.

GH may be appealing to athletics seeking an edge. It has a short half-life in circulation and its abuse is difficult to detect except in extremely high doses [52]. Increased IGF-1 stimulation by GH self-administration does not qualitatively differ from that which is supported by endogenous GH. Although synthetic GH contains just one molecular weight isoform, while endogenous GH secretion is a mix of 20kD and 22kD isoforms, it is rapidly cleared from the circulation and so testing needs to be done within hours after dosing [51,52].

Brennan et.al., [53] found in a study of performance-enhancing substance use among 231 experienced young male weightlifters that 27 (12%) of them reported illicit use of HGH or its bioactive derivative IGF-1. All of these 27 men also reported use of Anabolic-Androgenic Steroids (AAS) and 22 (81%) met criteria for current or past AAS dependence. Fifteen also reported current or past dependence on opioids, cocaine and/or ecstasy. These findings suggest that among young male weightlifters, illicit HGH use has become a common form of substance use, frequently associated with both AAS dependence and classical substance dependence.

Ben Johnson was one of several elite-class athletes who admitted to having taken GH for several years in combination with Anabolic-Androgen Steroids (AAS). The issue of GH abuse became a major problem in the Olympic Games in Sydney where large quantities of human GH were stolen from a whole-sale pharmacy [54]. The dose of GH abused by athletes varies but is said to be 10-25 IU/day, 3-4 times a week. Moreover, GH is taken for prolonged periods in cycles lasting 6-12 weeks [54]. There are major difficulties in detecting GH abuse. As stated before the 22 kD pituitary molecule of growth hormone and the recombinant human GH abused by athletes are identical. GH secretion is pulsatile and therefore the detection of an abnormally high value could simply be attributed to a spontaneous peak [55]. Moreover, exercise itself constitutes a major stimulus to GH secretion and IGF-1 levels increase in response to chronic exercise. GH secretion is also influenced by dietary habits such as the nutritional supplements favoured by a large number of athletes. Finally, the fact that only minute quantities of GH appear in the urine makes it very difficult to detect in this sample [54]. The recreational use of GH does not appear to be regulated by any governing agency. The real size of this market is largely unknown.

GROWTH HORMONE IN AGING AND ANTI-AGING

After achieving linear growth and full reproductive maturation GH levels begin to decline, primarily from reduced hypothalamic secretion of GH-releasing hormone, which leads to lower GH levels and reduction in serum IGF-1 levels. These normal age-related GH and serum IGF-1 reductions are associated with age-related changes that are similar to the signs and symptoms seen in GHD adults. Based on this decline and in alterations in body composition, strength and aerobic capacity that are also similar to those observed in adult GHD, though less severe, interest was raised in using GH therapy in healthy older patients. In 1990, Rudman et.al., [56] reported reduced fat mass,

increased muscle mass and increased lumbar vertebral bone density in healthy men, age 60 and older, after 6 months of GH use compared to untreated controls. Although no functional outcomes were reported this paper received wide publicity and led to subsequent studies looking to confirm the possible anti-aging benefits of GH in healthy seniors as well as rapid proliferation of anti-aging clinics offering GH to middle-aged as well as older clients, even in the absence of any confirmatory results.

Liu et.al.,[57] conducted a systematic review of 31 articles looking at 18 separate studies of GH treatment outcomes in healthy older individuals. They concluded that only minimal body composition changes (2,1 kg reduction in fat mass, 2,1 kg increase in LBM and 0,29 mmol/l reduction in total cholesterol) without significant change in bone density, other serum lipids or decrease in body weight was seen with GH use. However, a higher number of adverse events (edema, arthralgias, gynecomastia, development of impaired fasting glucose and diabetes) were reported.

Blackman et.al.,evaluated effects of GH and/or sex steroid treatment in older men and women in a 2-by-2 placebo controlled study. They reported that GH alone and GH with testosterone improved strength and exercise capacity whereas GH use alone did not. Adverse effects were similar with and without sex steroids except for a higher rate of fasting glucose intolerance or diabetes in men treated with GH only. These investigators initially attempted to use GH doses similar to those employed by Rudman et.al., [58] but were forced to reduce them by nearly 2/3 due to severe side effects. The reasons for the lack of side effects in the Rudman report are not clear [56,58].

Reports of effects of GH on BMD in non-GHD normal aging are conflicting.

Holloway et.al.,[59] found statistically significant improvement in BMD in postmenopausal women treated with GH, but concluded that the gains were substantially less than what is seen with bisphosphonates or estrogenic hormone therapy, with a higher incidence of adverse events. However, other studies did not demonstrate BMD increase with GH treatment in this population [60,61]. Metformin and GH did not appear to be superior to metformin alone in reducing total body fat or waist circumference in older patients with the metabolic syndrome and elevated fasting plasma glucose levels [62].

In a placebo-controlled study Baker et.al.,[63] demonstrated favourable effects on cognition in both healthy older adults and those with amnesic Minimal Cognitive Impairment (MCI) with 20 weeks of daily self-injection with a degradation-protected GHRH analog to boost GH secretion. Treatment with GHRH, which boosted GH secretion and IGF-1 levels, resulted in improvement in executive functioning and verbal memory. Visual memory was not enhanced. Though GHRH was generally well tolerated subjects on active treatment were twice as likely to have adverse effects, usually mild compared to those in the placebo arm. Thus, the use of GH to counter some effects of normal aging is still highly controversial. Most studies have shown some improvements in body composition, but failed to show an increase in cardiovascular endurance or muscle strength [57,58]. Additionally more adverse effects were reported in the GH treatment groups. Both the baseline and target differ from AGHD, with baseline levels lower than in young normals, but higher than in GHD. Target levels were above age-matched normals and similar to those in young adults. It is unclear if the mix of benefits and side effects and risks will be similar to those in AGHD, particularly

with use over longer durations than the maximum 1 year in current controlled studies.

Thus GH treatment in otherwise healthy seniors cannot be recommended other than in controlled clinical research studies. Its use for anti-aging purposes is currently prohibited by U.S. Federal Law 21 U.S.C. § 333 making GH the only legal drug for which off-label prescribing is illegal in two circumstances. The other prohibition is for use to boost athletic performance. The costs of monthly HGH injections in anti-aging are \$10,000/year. The offer of cheaper GH pills, sprays and patches on internet sites is near endless.

COST EFFECTIVENESS

Despite the positive effect of GH replacement treatment on body composition and markers of cardiovascular disease in adults with GHD it is difficult to measure the therapeutic benefits of GHRT with precision after linear growth has been completed. In addition, despite multiple studies, data showing that GHRT in GHD adults actually reduces mortality are still inconclusive [64].

Using Quality Adjusted Life Years (QALY) measures a cost-utility analysis of GHRT is feasible. Cost-utility analysis based on QALY change is the most widely recognized method in pharmacodynamic evaluation. In the U.K., the National Institute for Health and Clinical Excellence (NICE) serves as a potential source of outcomes data for such an evaluation [65]. In the U.S., many insurers have developed policies that set specific criteria for coverage of GH replacement in AGHD and to guide clinicians with appropriate dosing, monitoring and assessing cost effectiveness of GHRT. Some are evidence-based and follow the recommendations of the 2009 AACE or the 2011 Endocrine Society clinical practice guidelines, but others are arbitrary and in some cases at variance with best practices [66,67]. It appears at this time that cost-benefit data for GHRT favours treatment in clinical symptomatic patients with confirmed GHD.

The Pediatric Endocrine Society has issued new guidelines for treating children and adolescents with growth failure due to GH deficiency, ISS or primary IGF-1 deficiency in 2017 [7]. While GH therapy is evolving there are still important knowledge gaps. The long-term outcome on adult height is not known. In addition, hospitals and clinicians should adopt universal standardized IGF-1 and GH assays. For children with ISS, who do not have GH deficiency, the benefits of achieving taller stature via GH treatment are uncertain and of a lesser magnitude. Moreover, the high cost of GH therapy (U.S.\$ 35,000-50,000 per inch of height gained) is difficult to justify for those in whom it is unclear if there are benefits of treatments. In those situations parents and clinicians are advised to take a decision-sharing approach.

NEW TESTS FOR GH DEFICIENCY

Current dynamic testing procedures are either complex or attended with significant side effects or risks or both. Reliable and safe alternative diagnostic tests are therefore needed. Ghrelin is the natural GH secretagogue receptor ligand [68]. Stimulation testing using ghrelin mimetics was therefore a logical step forward. Conventional tests as the standard IGF-1 test cannot discriminate well between sufficient and insufficient GH secretion. The gold standard for the diagnosis is the insulin tolerance test. As this test is contra-indicated in the elderly and in patients with ischemic heart disease and seizures, it is regularly replaced by the GH-Releasing Hormone (GHRH)-arginine test which is well validated in adults.

Ghrelin has a strong GH-releasing activity by binding to the GH Secretagogue Receptor-type1 alpha (GHSR-1alpha) and can be used as a diagnostic test [68,69].

Blijdorp et al., examined 43 survivors of Subarachnoid Hemorrhage (SAH). Six out of 43 (14%) were diagnosed with GHD by GRHR-arginine test. In GHD subjects median GH peak during the ghrelin test was significantly lower than that of non-GHD subjects (5.4 vs 16.6; $p = 0.002$). Recover operating characteristics analysis showed an area under the curve of 0.869. A cutoff limit of a GH peak of 15 ug/l corresponded with a sensitivity of 100% and a false-positive rate of 40%. No adverse effects were observed in subjects undergoing a ghrelin test except flushing in one patient. Owing to its convenience, validity and safety the ghrelin test might be a valuable GH provocative test [69].

Recently, the FDA has approved the oral ghrelin agonist macimorelin (Macrilen) to be used in the diagnosis of patients with Adult Growth Hormone Deficiency (AGHD). Macrilen fills an important gap and addresses the need for a convenient test that is reliable, well-tolerated, reproducible, safe and simple. Stimulated GH levels will be measured over 90 minutes after administration of Macrilen through four blood samples [69-71].

POTENTIAL NEW BIOMARKERS IN GHD

A number of GH-responsive markers including metalloproteinases 2 and 9, vascular endothelial growth factor, isoforms of apolipoprotein and afamin have been identified [72-75]. The Growth Hormone Research Society recently concluded that the clinical endpoint in pediatric GH treatment is adult height with height velocity as a surrogate endpoint. Increased life expectancy is the ideal but unfeasible clinical endpoint of GH treatment in adult GH Deficient Patients (GHDA) and in patients with acromagaly. The pragmatic clinical endpoints in GHDA include normalization of body composition and quality of life, whereas symptom relief and reversal of co-morbidities are used in acromegaly [75].

IGF-1 is widely used as a biomarker, even though it correlates weakly with clinical endpoints in GH treatment, whereas in acromagaly normalization of IGF-1 may be related to improvement in mortality. There is an unmet need for novel biomarkers that capture the pleiotropic actions of GH in relation to GH treatment and in patients with acromegaly [75].

Recently, Tan et al., [76-79] investigated potential new biomarkers for the detection of human growth hormone administration in athletes by a proteomic approach to search for novel protein biomarkers associated with recombinant GH administration in non-elite athletes. In this study participants received either placebo or rGH for 8 weeks and were followed over a 6-week washout-period. Eight rGH-dependent proteins, namely apolipoprotein-L1, alpha-HS-glycoprotein, vitamin D-binding protein, afamin, insulin-like-growth factor-binding-protein-3, insulin-like growth factor-binding protein-ALS, lumican and extracellular matrix protein1 were identified. Apolipoprotein-L1 and alpha-HS-glycoprotein were validated by Western blots to confirm their identities and expression pathways in rGH and placebo-treated subject cohorts. Independent confirmation of these putative GH-response biomarkers would be of value and may have sports antidoping utility.

CONCLUSION

Studies in adult GHD have shown that GH is more than simply a "growth hormone" so that it should appropriately be renamed

“somatotrope hormone”. Its strong influence on body composition, metabolism and structure function, including CNS functions such as sleep has amply been investigated. 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 available evidence GH cannot recommended for use by the healthy elderly bearing in mind that GH decline with age may represent a beneficial adaptation to ageing. New GH stimulation tests and putative new GH biomarkers might shed light on this debate in the future. These new biomarkers might also improve doping testing for GH which is still difficult and not optimal. GH research has a bright future when microfluidic hybrid delivery systems will become available as a result of the fusion of biochemistry, biology and nanotechnologies.

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