COMPARISON OF INFLUENCE OF LONG-ACTING GROWTH HORMONE (LAGH) VS DAILY GROWTH HORMONE SUBSTITUTION ON PATIENT-REPORTED OUTCOMES AND COGNITIVE FUNCTIONS IN GH-DEFICIENT PATIENTS: A PROTOCOL

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Abstract:
Objective: The goal of this study is to analyze the influence of growth hormone (GH) replacement (daily versus long acting) on patient-reported outcomes (i.e., quality of life, health status and well-being) and cognitive functioning in GH-deficient adults by systematic review of the published clinical trials.

Design: A meta-analysis of clinical trials concerning the influence of GH substitution on patient-reported outcomes and cognitive functions (studies will be selected from 2000 to 2022). The results of individual studies will be combined in a series of meta-analyses using a random effects model. Effects of GH replacement (daily versus long acting) in GH-deficient adults will be compared.

Expected outcome: This meta-analysis may provide an evidence of a better GH analogue (daily Vs long acting) in improving patient-reported outcomes in GH-deficient patients. As the amount of cognitive data is too limited to allow for comparisons with the two analogues of GH, conclusions may be drawn with respect to the impact of GH daiy vs long acting) treatment on cognition.

Keywords: Long-acting growth hormone, quality of life, growth hormone deficiency

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DOI: 10.48047/ecb/2023.12.si10.00202

Introduction

Emerging data indicate that growth hormone (GH) therapy could have a role in improving cognitive function. GH replacement therapy in experimental animals and human patients counteracts the dysfunction of many behaviors related to the central nervous system (CNS). Various behaviors, such as cognitive behaviors related to learning and memory, are known to be induced by GH; the hormone might interact with specific receptors located in areas of the CNS that are associated with the functional anatomy of these behaviors. GH is believed to affect excitatory circuits involved in synaptic plasticity, which alters cognitive capacity. GH also has a protective effect on the CNS, as indicated by its beneficial effects in patients with spinal cord injury. Data collected from animal models indicates that GH might also stimulate neurogenesis.

Clinical experience of GH replacement therapy in children and adults with GH deficiency has provided substantial evidence that this therapy is safe and well tolerated [1,2]. However, some concerns remain about the efficacy of using GH as a cognitive enhancer owing to conflicting results in the literature. Several studies have convincingly shown that individuals with GH deficiency show cognitive impairment, which can be ameliorated by treatment with GH [3-6]. For instance, GH replacement therapy prevented deterioration of certain skills related to cognition in children with Prader–Willi syndrome in the short term and strongly improved abstract reasoning and visuospatial skills over a period of 4 years in these children [6]. However, some studies have reported no statistically significant changes in cognitive function or QoL following GH replacement therapy in elderly people [7,8]. Furthermore, no association between a previous excess of GH and poor cognition was seen in patients with acromegaly [9]. These negative results might be explained by the different conditions that were included in the studies, but could also be associated with the more pronounced effects of GH on certain components of cognitive function.

Multiple LAGH preparations are currently at various stages of development allowing for decreased GH injection frequency from daily to weekly, bi-weekly, or monthly. Following administration of LAGH, the serum peak and trough GH and IGF-I levels vary depending upon the mechanism used to prolong GH action. Randomized, controlled clinical trials of some LAGH preparations have reported non-inferiority compared to daily recombinant human GH (rhGH) for improved growth velocity and body composition in children and adults with GH deficiency (GHD), respectively. The goal of the study is to compare the effectiveness of both the GH analogues, daily Vs long acting in improving the cognitive functions of adults with growth hormone deficiency, in terms of patient-reported outcomes and quality of life, by meta-analysis.

Growth hormone deficiency (GHD) is a well-defined clinical syndrome, observed both in children and in adults. Symptoms of GHD are decreased lean body and muscle mass, increased fat mass, reduced bone mineral density, lipid profile changes and psychiatric symptoms [10]. Growth hormone (GH) substitution in adults with GHD has been found to improve body composition, bone mineral density, lipid profile, mood and cognitive function [11–13]. Decreased GH–insulin like growth factor 1 (IGF-I) levels are observed in GH-deficient adults and children, but also in normal aging. Features of aging resemble those of GHD, suggesting that the GH–IGF-I axis may play a role in age-related cognitive decline [14].GH-deficient patients can be subdivided in two different types of patients, namely those with GHD present from birth or early childhood (childhood-onset GHD, CO-GHD) and those with a decreased pituitary function starting later in life (adult-onset GHD, AO-GHD). Another distinction concerns the extent of the pituitary failure: isolated GHD (IGHD), in which only the GH secretion is insufficient and multiple hormone deficiencies (MPHD), in which there is GHD and also an impaired secretion of other pituitary hormones.

At present there is accumulating evidence that GH and IGF-I play an important role in cognitive functioning and quality of life (QoL), heath status and wellbeing, which three last concepts will be covered by the term ‘‘patient-reported outcomes’’. Although the exact mechanism of the action of GH–IGF-I on the brain including the relation between the GH–IGF-I axis and psychological parameters is not fully known yet, there is evidence that GH and IGF-I can cross the blood–brain barrier [15] and that binding sites for GH and IGF-I exist in the choroid plexus, hypothalamus, putamen, thalamus and hippocampus [16,17]. GH substitution in GH-deficient adults increased levels of IGF-I and IGFBP-3 in the cerebral spinal fluid (CSF) [18]. In addition,it has been found that GH significantly affects neural cell metabolism in adult men. This is concluded from changes in cerebrospinal fluid concentration of the dopamine

metabolite homovanillic acid observed after GH treatment [15]. It is known that high levels of dopamine are present in the hippocampus, a structure that plays an important role in learning and memory. Therefore, a change in the availability of GH in the hippocampus may influence memory processes by altering the dopamine turnover in this area [19].

Hormones may influence brain function by affecting early brain development in uterus or by changing peripheral and neural processes temporarily [20]. As mood and memory impairment in GHD can be normalized by GH treatment [13,21], mood and cognitive impairments in GH-deficient patients are most likely associated with a reversible GH-specific disturbance in neural cell metabolism and not with an abnormal brain development. With respect to the relation of GH with mood state, it is known that patients with GH excess (seen as acromegaly or gigantism) show fluctuations in mood [22,23]. GH, however, exerts its influence on the brain in collaboration with other hormones. For instance, excess of cortisol is known to have negative emotional effects, as anxiety and nervousness, and cortisol- deficient patients suffer from subnormal cognitive functioning and a reduced energy level. In addition, sex hormones (i.e., testosterone and oestrogen) are known to have influence on behavior and also excess or deficiency of thyroid hormone may cause mental disturbances, such as depression or mania [24]. As GH influences the levels of these hormones, mood and cognitive disturbances in patients with GHD may be directly related with GHD or indirectly by abnormal levels of these hormones.

Hormone replacement is a standard therapy in the treatment of pituitary insufficiency. There is however some difficulty in accepting GH treatment as a standard procedure, caused by the high costs of GH therapy combined with a lack of consensus on the beneficial consequences of GH substitution in adults. At present a major problem in evaluating GH effects on QoL is the lack of conformity between study findings. Most studies are performed with a relatively small number of patients, with a variety of instruments in heterogeneous patients groups (gender, age, duration of GHD, medical history, etc.) and most studies lack a control group. A main problem arises in the different definitions used to describe QoL. Smith et al [25], for instance, defined QoL as the subjective appraisal of ones current life based primarily on psychological function and to a lesser degree on physical functioning. However, some authors not even describe the definition of QoL used in their study. In addition, the lack of conceptual clarity concerning QoL frequently lead to inappropriate assessment of this concept. With regard to GHD, a subnormal QoL in adults with GHD is inferred from the observations that these patients feel less energetic, are emotionally more labile, and experience disturbances in sex life and feelings of social isolation at a significantly higher frequency than controls [26-29]. Indeed, a lot of measures described as QoL questionnaires in these studies, do not always measure QoL, but health status or psychological well-being. Therefore, we will use the term ‘‘patient-reported outcomes’’ to indicate QoL, health status and psychological well-being.

The objective of this meta-analysis is to evaluate the effects of daily GH Vs LAGH substitution on patient-reported outcomes and cognitive functions in terms of quality of life in GH-deficient adults by analyzing and pooling the effects of all relevant studies on this topic.

Project Design and Methods

***i (a). Implementation*:**

Core Project Components:

Step 1: defining the research question
Step 2: literature search
Step 3: choice of the effect size measure
Step 4: choice of the analytical method used
Step 5: choice of software
Step 6: coding of effect sizes
Step 7: analysis
Step 8: reporting results

Search strategy

Electronic databases PUBMED, google scholar, CNKI will be searched from 2000 to 2012. Studies that evaluated the effect of GH Vs Long-acting growth hormone (LAGH) on cognitive functioning or patient-reported outcomes in adults with GHD (aged 18 years and above) will be included. The search terms used will be: growth hormone, memory, mood, cognition, well-being and quality of life.

Study selection

Two investigators will be independently examining the manuscripts for inclusion. Eligible studies will be reports providing quantitative data about the effect of LAGH Vs daily GH therapy on cognitive functioning or patient-reported outcomes in GH-deficient adults.

Studies will be controlled or designed as a cross-

over/parallel or open clinical trials with LAGH Vs daily GH. Questionnaires used are those which measure patient-reported outcomes and neuropsychological tests for assessing cognitive functioning.

Exclusion criteria: Case reports, review articles and studies in which the
psychometric quality of the used questionnaire or test are unknown will be excluded. Furthermore, studies on GH therapy for other diseases (for instance Turner syndrome, Prader Willi Syndrome, fibro-myalgia, etc.) will not be included in this meta-analysis.

Measurements of patient-reported outcomes

The following paragraph describes the most frequently used questionnaires measuring QoL, health status or well-being encountered in the studies included in the meta-analysis.

The Nottingham Health Profile (NHP) health status questionnaire in GH-deficient patients will be used that measures physical, emotional and social distress. It consists of the subscale's emotional reactions, energy, pain, physical mobility, sleep and social isolation [30]. The Psychological General Well Being Schedule (PGWB) measures self-perceived affective and emotional states [31]. Subscales include anxiety, depressed mood, positive well-being, self-control, general health and vitality. The Hopkins Symptom Checklist (HSCL) is a questionnaire for the assessment of psychological and somatic complaints [32]. The Profile of Mood States (POMS) is a 32-item questionnaire with subscales depression, anger, fatigue, vigour and tension [33] and the State-Trait Anxiety Inventory (STAI) is a questionnaire to assess state and trait anxiety [34]. The Quality-of-Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) [35] is especially designed to assess relevant aspects of GHD.

Cognitive functions

In the studies included in the meta-analysis a variety of cognitive tests will be used to measure short- and long-term memory, comprehension, vocabulary, verbal fluency and non-verbal skills. Short-term memory was assessed by the associate learning task [36] and the ten-word task [37]. The associate learning recognition task, ten-word test recall and recognition task assessed long-term memory. Other tests measured iconic memory (the capacity to process a flash of information), picture arrangement, vocabulary, comprehension, verbal fluency and the non-verbal Wechsler Adult Intelligence Scale (WAIS) test [38].

Statistical analysis

A series of meta-analyses statistical analysis will be carried out using a random effects model. The meta-analyses will be performed using the statistical package Comprehensive Meta-analysis (Biostat, Inc., USA). This program is used to determine d-values (effect sizes). The most commonly used measures of effect size are the standardized mean difference (d) and the correlation coefficient (r). The effect size is a simple quantitative measure that provides one useful index of the importance of an effect. The effect size index d standardizes the raw effect size as expressed in the measurement unit of the dependent variable by dividing it by the common SD of the measures in their respective Populations [39]. The difference prior to and after GH Vs LAGH therapy or between active treatment and placebo, divided by the pooled standard deviation of the two measurements or group means will be calculated. Effect sizes (ds) will be calculated, averaged for each study and pooled. Effect size d = 0.2 is defined as a small effect, d = 0.5 as a medium effect and d = 0.8 as a large effect. A medium effect size is conceived as one large enough to be visible to the naked eye[39]. The test for heterogeneity will be carried out by the Q test.

Conclusion

It is expected that this meta-analysis may show that LAGH Vs improves patient-reported outcomes and cognitive functioning in patients with GHD as compared to those on daily GH therapy. LAGH therapy may be more effective than daily acting GH treatment. The results of this meta-analysis may contribute to decisions on administration of long acting Vs daily GH in adults with GHD.

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