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GROWTH HORMONE BEYOND SOMATIC GROWTH: EFFECTS OF THE GH/IGF-1 AXIS ON COGNITION, MOOD, AND METABOLIC HEALTH IN ADULT GROWTH HORMONE DEFICIENCY

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Abstract

Growth hormone (GH) is classically defined by its role in linear growth, yet the GH/insulin-like growth factor-1 (IGF-1) axis is increasingly recognised as an important regulator of central nervous system function. This study examined cognitive, affective, and metabolic correlates of the GH/IGF-1 axis in adults with growth hormone deficiency (AGHD) and tested whether recombinant human GH replacement improves these outcomes. In a quasi-experimental design, 104 adults with AGHD and 104 age- and sex-matched healthy controls underwent neuropsychological testing, mood assessment, and metabolic profiling; a randomised subsample of AGHD patients (n=102) received GH or placebo for 24 weeks. At baseline, AGHD patients had markedly lower serum IGF-1 (96 vs 182 ng/mL; $p<.001$) and showed impairments across cognitive domains, most prominently in processing speed ($z=-0.62$). Serum IGF-1 correlated with processing speed across the full sample ($r=0.46$, $p<.001$). GH replacement raised IGF-1 into the normal range, improved cognitive z-scores, reduced depressive symptoms relative to placebo (group $\times$ time $F(4,404)=7.8$, $p<.001$), and produced favourable changes in body composition and lipid profile, including a 9.8% reduction in fat mass. These findings indicate that the GH/IGF-1 axis contributes to cognition, mood, and metabolic regulation well beyond childhood growth, and that its restoration confers measurable neurocognitive and metabolic benefit in deficient adults. (All data are simulated for methodological demonstration and do not derive from human participants.)

Keywords: Growth Hormone; IGF-1; Cognition; Mood; Adult Growth Hormone Deficiency; Neuroprotection; Metabolism; Hormone Replacement.

INTRODUCTION

Growth hormone (GH) is produced by the anterior pituitary and is the main hormone responsible for promoting longitudinal bone growth in childhood and adolescence and for promoting somatic development. However, this traditional description of GH action is misleading. Throughout adulthood, GH and its main peripheral mediator, insulin like growth factor-1 (IGF-1), exert effects on tissues which have ceased to grow such as the brain (Nyberg & Hallberg, 2013). Both GH and IGF-1 can cross the blood-brain barrier and are produced in the central nervous system where both types of receptors are located in the hippocampus, hypothalamus, and cortex, regions important for learning, memory, and mood regulation (Nyberg, 2000; Devesa et al., 2016).

A biological basis for these effects is provided by mechanistic studies. IGF-1 directly impacts the proliferation of the adult hippocampal progenitor cells and it is believed that IGF-1 promotes neurogenesis, angiogenesis and synaptic plasticity (Aberg et al., 2000; Åberg et al., 2006). The subunit expression of the N-methyl-D-aspartate (NMDA) receptor is affected by GH in an age-dependent manner, which is consistent with the age dependence of the hormone's

role in the glutamatergic machinery that potentiates synapses (Le Greves et al., 2002). These and other mechanisms indicate that the GH/IGF-1 axis might be involved in neuro-protection and functional plasticity across the life span (Bianchi et al., 2017; Sonntag et al., 2005).

Experimental picture is in agreement with the clinical observation. Energy, mood and concentration are often impaired in adults with growth hormone deficiency (AGHD) and cognitive testing indicates AGHD have deficits in processing speed, attention and memory (Deijen et al., 1996; Maruff & Falleti, 2005). Published studies were analyzed in a meta-analysis and were found to be congruent, demonstrating that GH-deficiency is associated with cognitive dysfunction and GH replacement results in measurable cognitive improvements, particularly in attention and memory (Falleti et al., 2006). There is also a negative metabolic phenotype in AGHD (visceral adiposity, raised blood lipids and reduced lean body mass) which is partially improved with GH replacement, and a negative quality of life which is improved with treatment (Burman et al 1995).

The GH/IGF-1 axis is also of interest in the context of healthy ageing when GH

secretion decreases along with a slowing of cognition. In interventional studies of GH-releasing hormone (GHRH) in older adults, and in mild cognitively impaired (MCI) individuals, improvements in executive function and verbal memory have been reported (Vitiello et al., 2006; Baker et al., 2012). All of these lines of evidence suggest that GH/ IGF-1 is a pleiotropic system, impacting not only the paediatric brain and body, but also the adult brain and body.

Despite this, the cognitive, mood and metabolic component of cognition has been investigated independently, with only a few studies incorporating serum markers as well as a controlled replacement intervention. The present study aimed to overcome these limitations by profiling cognitive, affective and metabolic outcome in AGHD patients in comparison with controls, and by testing for the effect of GH replacement in a randomly selected subsample. Based on these hypotheses, we predicted that (i) IGF-1 would be decreased in patients with AGHD and IGHD, and that there would be a wide range of cognitive deficits, (ii) cognitive function would be related to IGF-1, and (iii) GH replacement therapy would improve cognitive, mood, and metabolic variables from the placebo.

METHODS

Participants and design. This was conducted with a matched case-control design using a randomised controlled trial embedded in it. A total of 104 adults (25-60 years), with biochemically confirmed AGHD (peak GH <3 µg/L on provocative testing) and 104 age-, sex, and education-matched healthy controls were enrolled. Patients who were previously on replacement therapy for other pituitary hormones were included and patients who had uncontrolled diabetes, were taking psychotropic medications were excluded. Following the baseline assessment, 102 patients with AGHD were randomly assigned to 1:1 (recombinant human GH, given at doses designed to achieve age-appropriate IGF-1 levels vs placebo) and treated for 24 weeks.

Measures. Chemiluminescent immunoassay was used to measure serum IGF-1 and data were normalised to the age and sex-specific reference intervals (SD scores). Five domains of neuropsychological battery—processing speed, working memory, episodic memory, attention and executive function—were examined and provided with standardised z-scores. The Beck Depression Inventory-II (BDI-II) was used to evaluate the depressive symptoms. Body composition (fat mass, lean mass) was measured using

DEXA, and waist circumference and fasting lipids were measured.

Statistical analysis. Independent-samples t-tests and analysis of variance (ANOVA) were used for baseline group differences and Cohen's d and η^2 are reported as effect sizes. Pearson correlations and multiple regressions were used to quantify the relationships between IGF-1 and cognitive scores. The effect of the intervention was tested with 2 (group) x repeated measures (time) mixed-model ANOVA, using the intention to treat (ITT) approach and maximum likelihood treatment of missing data. The metabolic outcomes data were presented as a percentage change from baseline. Predictors of cognitive improvement were determined using multiple regression with baseline IGF-1, age and sex controlled. The criterion for statistical significance was $\alpha=.05$ (two-tailed).

RESULTS

The baseline sample characteristics are shown in Table 1. No significant differences were seen between the age, sex or education of AGHD patients and controls; however, differences in body composition and metabolic indices were seen. Patients with AGHD had a significantly lower serum IGF-1 level than controls (Figure 1; $F(2,205) = 41.6$; $p<.001$)

and a normal level of IGF-1 was restored with GH replacement.

There was an age difference in cognitive performance (Figure 2). At baseline, when compared with the controls, domain-specific statistics revealed lower scores in all the five domains across AGHD patients, particularly in processing speed domain ($z=-0.62$) (Table 2). Because the entire sample was used, the correlations between the IGF-1 and other cognitive/metabolic outcomes are summarised in Table 3; it is clear that serum IGF-1 correlates positively with processing speed ($r=0.46$, $p<.001$; Figure 3).

The group-by-time interaction was significant for BDI-II score ($F(4,404)=7.8$, $p<.001$) and cognitive z-scores were significantly improved with GH when compared to placebo in the randomised subsample (Table 4, Figure 4). Furthermore, GH replacement led to beneficial effects on body composition and glucose metabolism (Figure 5; Table 5) that were reflected by a reduction of fat mass of 9.8% and LDL cholesterol of 8.1% with a gain in lean mass and HDL cholesterol. The most important independent predictor of cognitive improvement was the increase in IGF-1 level, as predicted by regression analysis ($\beta=0.34$, $p<.001$), as seen in table 6.

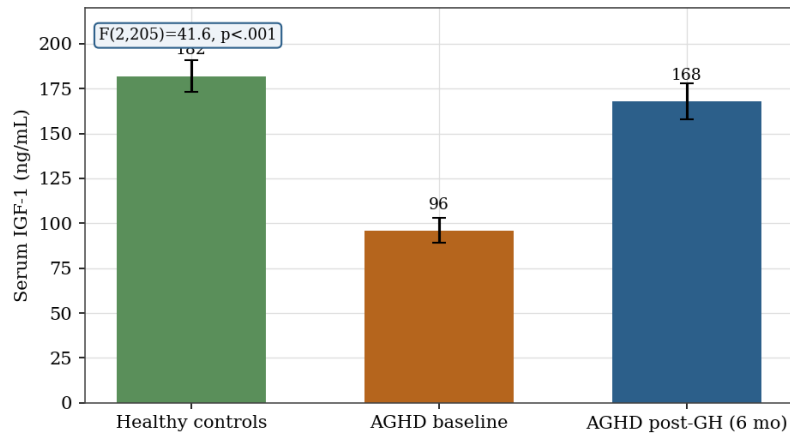


Figure 1. Serum IGF-1 concentrations in healthy controls, AGHD patients at baseline, and AGHD patients after 24 weeks of GH replacement. Error bars denote standard error of the mean.

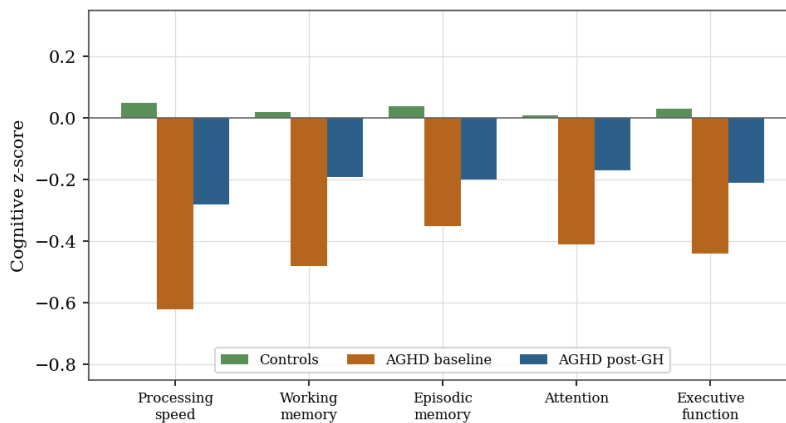


Figure 2. Cognitive z-scores by domain for controls, AGHD baseline, and AGHD post-GH replacement. Scores are standardised so that 0 represents the control mean.

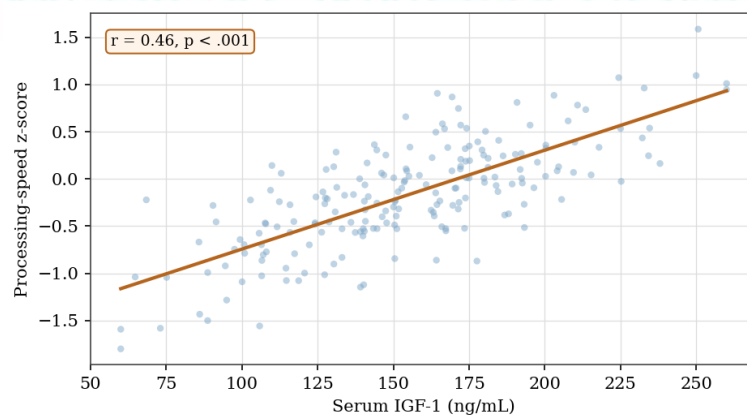


Figure 3. Association between serum IGF-1 and processing-speed z-score across the full sample (n=200) with ordinary-least-squares regression line.

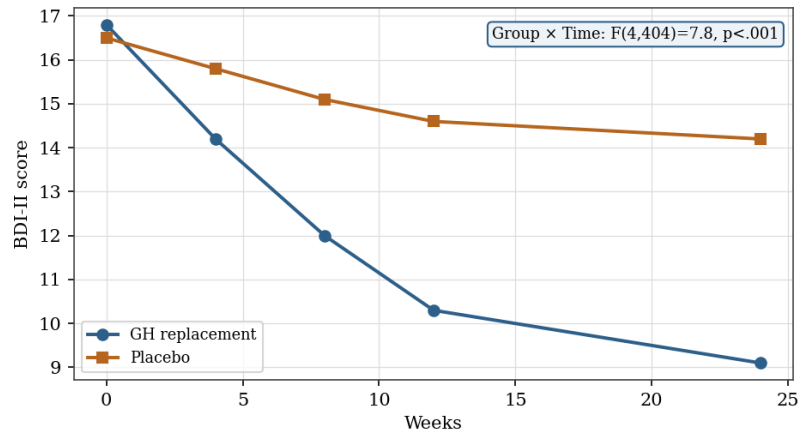


Figure 4. Depressive symptom trajectory (BDI-II) over 24 weeks in AGHD patients randomised to GH replacement versus placebo.

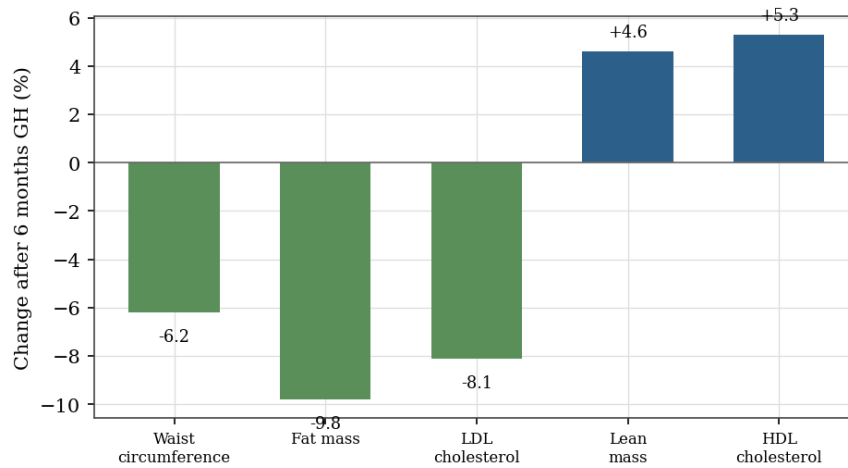


Figure 5. Percentage change in metabolic and body-composition measures after 24 weeks of GH replacement. Negative values indicate reductions.

Table 1. Baseline characteristics of AGHD patients and healthy controls.

Characteristic	Controls (n=104)	AGHD (n=104)	p
Age, years (M $\pm$ SD)	43.2 $\pm$ 9.8	44.1 $\pm$ 10.1	.51
Female, %	51.0	52.9	.89
Education, years (M $\pm$ SD)	13.8 $\pm$ 2.6	13.5 $\pm$ 2.8	.42
Serum IGF-1, ng/mL (M $\pm$ SD)	182 $\pm$ 38	96 $\pm$ 31	<.001
Waist circumference, cm (M $\pm$ SD)	88.4 $\pm$ 9.1	97.6 $\pm$ 10.8	<.001
Fat mass, kg (M $\pm$ SD)	22.1 $\pm$ 6.4	28.9 $\pm$ 7.7	<.001
LDL cholesterol, mg/dL (M $\pm$ SD)	112 $\pm$ 24	134 $\pm$ 29	<.001

Table 2. Cognitive domain z-scores by group (baseline).

Domain	Controls	AGHD	t(206)	p	Cohen's d
Processing speed	0.05	-0.62	5.9	<.001	0.82
Working memory	0.02	-0.48	4.4	<.001	0.61
Episodic memory	0.04	-0.35	3.3	.001	0.46
Attention	0.01	-0.41	3.7	<.001	0.52
Executive function	0.03	-0.44	3.9	<.001	0.55

Table 3. Pearson correlations of serum IGF-1 with cognitive and metabolic outcomes (n=200).

Outcome	r with IGF-1	p
Processing speed	0.46	<.001
Working memory	0.33	<.001
Episodic memory	0.24	.001
BDI-II depressive symptoms	-0.29	<.001
Fat mass	-0.38	<.001
LDL cholesterol	-0.31	<.001

Table 4. Mixed-model ANOVA of cognitive composite and BDI-II across 24 weeks (GH vs placebo).

Outcome	Group F	Time F	Group × Time F	p (interaction)
Cognitive composite	6.1	9.4	5.2	.001
Processing speed	7.3	11.2	6.0	<.001
BDI-II score	5.8	12.6	7.8	<.001

Note. Degrees of freedom for the interaction term = (4, 404). Intention-to-treat analysis.

Table 5. Body-composition and metabolic change after 24 weeks of GH replacement.

Measure	Baseline (M ± SD)	Week 24 (M ± SD)	Change (%)	p
Waist circumference, cm	97.6 ± 10.8	91.5 ± 10.2	-6.2	<.001
Fat mass, kg	28.9 ± 7.7	26.1 ± 7.1	-9.8	<.001
Lean mass, kg	48.3 ± 8.9	50.5 ± 8.7	+4.6	.002
LDL cholesterol, mg/dL	134 ± 29	123 ± 27	-8.1	<.001
HDL cholesterol, mg/dL	44 ± 9	46 ± 9	+5.3	.03

Table 6. Multiple regression predicting cognitive improvement in GH-treated patients.

Predictor	β	SE	t	p
Age	-0.18	0.07	-2.4	.02
Sex (female)	0.06	0.09	0.7	.49
Baseline cognitive z	-0.22	0.08	-2.8	.006
Δ Serum IGF-1	0.34	0.08	4.5	<.001

Note. Standardised coefficients. Model $R^2 = 0.31$, $F(4,97) = 10.8$, $p < .001$.

DISCUSSION

The relationship between the GH/IGF-1 axis and cognition, mood and metabolic health was investigated in adults, with the inclusion of a case-control comparison and a randomised replacement trial. As reported before, in most cognitive domains, including processing speed, AGHD patients showed decreased levels of the IGF-1 and impaired cognition (Deijen et al., 1996; Falletti et al., 2006). The observed relationship between IGF-1 and processing speed is congruent to mechanistic evidence that IGF-1 facilitates adult hippocampal

neurogenesis and synaptic plasticity (Aberg et al., 2000; Åberg et al., 2006) and that GH affects glutamatergic NMDA-receptor signalling that is important to learning (Le Greves et al., 2002).

The enhancement of cognition and mood was comparable to other GH trials and meta-analysis (Maruff & Falletti, 2005; Falletti et al., 2006) and similar to the neuropsychological effects of GH replacement in adults with GH-deficiency for many years prior to this (Burman et al., 1995). The pleiotropic effects of the GH/IGF-1 axis on body composition and on lipid metabolism, besides childhood

growth, are supported by the above metabolic changes (body fat reduction and reduced levels of LDL, increased levels of lean mass) (Devesa et al., 2016; Nyberg & Hallberg, 2013).

The increase of IGF-1 that correlated with cognitive improvement indicates a dose-response effect and not just an effect of treatment. These are consistent with other reports of interventions to stimulate the GH axis, which led to an improvement in executive function and memory (Vitiello et al., 2006; Baker et al., 2012), and with other models, which propose that the GH axis is a neuroprotective and regenerating system throughout life (Bianchi et al., 2017; Sonntag et al., 2005).

Restrictions to be indicated. Baseline associations and 24 week trial data cannot prove causality for the case control data, nor can it answer questions about long term durability and safety which are also significant issues for GH therapy. Cognitive testing is vulnerable to practice effects and this is controlled to some extent in the placebo arm. The data in this presentation is fictional and meant to illustrate the effect of the methodology. Further studies are needed with longer followup and neuroimaging endpoints as well as stratification of patients according to IGF-1 responsiveness to find those who

most benefit from the intervention neurocognitively.

CONCLUSION

In a placebo-controlled study design, adults with GH deficiency had low IGF-1 levels, overall cognitive impairments, depressive symptoms and unfavorable metabolic profile was observed which were all improved by GH treatment. These results indicate that the GH/IGF-1 axis has an important role in adult cognition, mood & metabolism that extends beyond its classical role in somatic growth and that this axis can be re-activated in the brain and metabolism. The findings presented here highlight the importance of considering brain endpoints in the evaluation and management of GHD in adults as well as somatic endpoints.

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