

## Psychological functioning after growth hormone therapy in adult growth hormone deficient patients: endocrine and body composition correlates

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**Key words:** growth hormone, growth hormone deficiency, mood, cognition, quality of life.

**Summary.** Growth hormone replacement in adult growth hormone deficient patients improves psychological well-being and the quality of life. The aim of this study was to investigate relationship between changes in mood, cognitive functioning, quality of life, changes in body composition and hormone concentration at baseline and six months after treatment with human recombinant growth hormone. Eighteen adult patients with growth hormone deficiency syndrome were recruited to the study. Growth hormone was administered in doses of 12 IU per week in an open design. After 6 months of growth hormone replacement therapy the psychological functioning improved significantly on mood scales (Profile of Mood State) and on a cognitive performance tests. Changes in quality of life scale were trivial. After growth hormone treatment serum concentration of Insulin like growth factor -1 (IGF-1) and triiodothyronine increased and concentration of serum free thyroxine decreased significantly in comparison to basal concentration. There were no significant differences in changes of plasma cortisol, thyrotropin and growth hormone concentrations. Improvement on Profile of Mood State global score as well as on Vigor-Activity subscale correlated significantly with increase in IGF-1 concentration. Improvement on Profile of Mood State Vigor-Activity subscale correlated with increase in water body mass and improvement on Hospital Anxiety and Depression scale depression subscale correlated with decrease in cortisol concentration.

The study shows that growth hormone replacement improves mood and cognition in adult growth hormone deficient patients. This improvement is related to changes in water body mass as well as to endocrine changes.

### Introduction

Growth hormone (GH) deficiency syndrome in adults consists of physical and mental symptoms (1). Mental symptoms most frequently observed in patients with GH deficiency include lack of energy, depression and cognitive dysfunction. Decreased quality of life is also frequently reported (2). Improvement in quality of life after replacement therapy with recombinant human GH was demonstrated in GH deficient patients (2, 3). The quality of life assessment is the measure designed to evaluate broad social and psychological well-being of the patient, covering cognitive and mood symptoms only superficially. Impaired cognitive functioning has been reported in GH deficient patients (4) and this impairment improves after GH treatment (5). Very few studies have used adequate mood rating instruments to assess depressive symptoms in patients with GH deficiency as well as changes in mood state

after replacement therapy (6, 7).

In the present open design study we investigated changes in mood, cognitive state and quality of life at baseline and six months after treatment with human recombinant GH in eighteen adult patients with GH deficiency syndrome in relation to changes in endocrine function and body composition.

### Material and methods

Eighteen GH deficient patients (9 men and 9 women) with a mean age of  $28.9 \pm 5.7$  years (range 21–40) were included into the study. Seventeen patients had multiple pituitary hormone deficiencies; one had isolated GH deficiency. In all patients the diagnosis of GH deficiency had been established in childhood. Thirteen patients had received GH therapy for several years. However, for at least five years immediately to the study none had received GH replacement. In 14

patients conventional hormonal replacement included oral thyroxine, started at least four months before the study. Before inclusion in the study the hormonal status of each subject was reevaluated by detecting serum insulin-like growth factor-1 (IGF-1) and the peak GH response to insulin-induced hypoglycemia. The study protocol was approved by the Medical Ethical Committee of Kaunas University of Medicine. All subjects of the study gave informed consent.

The study used an open design. Assessment of each patient was performed at baseline and six months after GH replacement. Human recombinant GH (Biofa, Lithuania) was administered in doses of 12 IU per week subcutaneously (2 IU six times a week) for 6 months. The structure of the GH, used in this study, differs from natural human GH by lack of amino acid phenylalanine in the N- end of the molecule.

All hormone concentrations were assayed by commercial kits. Serum thyrotropin (thyroid stimulating hormone, TSH) concentration was estimated by means of ultrasensitive immunoradiometric assay. Serum GH, cortisol, free thyroxine (FT<sub>4</sub>) and triiodothyronine (T<sub>3</sub>) were estimated by means of radioimmune assay. Body composition was assessed by use of a body composition monitoring unit Bodystat 1500 (Great Britain).

Hospital Anxiety and Depression (HAD) scale (8) and the Profile of Mood States (POMS) (9) were used for the assessment of mood state. Cognitive state was assessed by use of the Digit Symbol Test (DST) and the Digit Span Subset (DSS) of the Wechsler (10) Adult Intelligence Scale. Quality of life was evaluated by the means of Quality of Life Assessment of GH Deficient Adults (QoL-AGHDA) scale (11, 12).

Descriptive values are given as a mean ± standard deviation. The differences between baseline measurements and measurements after six months of GH treatment were compared using Wilcoxon signed rank test. In all calculations we considered p values <0.05 as significant, but values between p=0.05 and p=0.1 are reported. Spearman's correlation coefficient was used for evaluating the relationship between two variables.

**Results**

Table 1 shows changes in hormone concentrations and body composition six months after GH therapy. Significant changes were observed in IGF-1 concentration as well as in thyroid hormone levels. IGF-1 concentration more than doubled from baseline. Concentration of triiodothyronine increased and concentration of thyroxine decreased significantly after GH replacement. There was no significant change in concentration of GH, cortisol and TSH. Significant increases in body mass index (BMI), lean body mass and water body mass were observed after GH treatment.

Table 2 shows changes in psychological functioning. On most scales there was improvement in mood and cognition after GH treatment. Statistically significant differences were observed on Profile of Mood State and on scores of Digit symbol test.

Significant correlations occurred between changes in psychological functioning and change in body composition as well as in change of hormone concentration after six months of GH treatment. Mood improvement on POMS global score and Vigor-Activity subscale was strongly related to increase in IGF-1 concentration (r=0.50, p=0.04 and r=0.45, p=0.06, respec-

**Table 1. Serum hormone concentrations and body composition at baseline and after six months of growth hormone therapy in 18 adult growth hormone deficient patients**

Serum hormone concentrations and body composition	Baseline	After 6 months treatment	Wilcoxon p values
Triiodothyronine (nmol/l)	0.8±0.4	1.3±0.6	0.04
Free thyroxine (pmol/l)	13.8±3.3	11.4±4.8	0.03
Thyrotropin (IU/l)	1.0±1.3	0.8±0.8	Ns
Cortisol (nmol/l)	229±157	199±147	Ns
Growth hormone (ng/ml)	0.3±0.2	0.3±0.3	Ns
Insulin-like growth factor-1 (ng/ml)	41.6±27.0	90.9±51.7	<0.001
Body mass index	24.1±3.0	24.7±3.4	0.04
Lean body mass	39.8±12.6	40.7±11.8	0.09
Fat body mass	16.4±4.0	16.7±5.7	Ns
Water body mass (Means ± SD)	28.2±5.6	30.1±5.6	0.02

Ns – not significant.

**Table 2. Psychological scores at baseline and after six months of growth hormone therapy in 18 adult growth hormone deficient patients**

Profile of Mood State	Baseline	After 6 months treatment	Wilcoxon p values
Global score:	25.1±20.6	18.3±27.3	0.04
– Tension-Anxiety	6.8±1.0	5.7±1.1	Ns
– Depression-Dejection	11.2±1.7	10.7±2.0	Ns
– Anger-Hostility	8.3±1.4	8.0±1.9	Ns
– Vigor-Activity*	12.6±1.1	14.6±1.1	0.08
– Fatigue-Inertia	7.5±0.7	6.0±1.0	0.07
– Confusion-Bewilderment	3.8±0.9	2.5±1.0	0.04
Hospital Anxiety and Depression Scale:			
– Depression	4.8±4.0	4.2±3.0	Ns
– Anxiety	6.3±3.2	5.5±3.7	Ns
Digit Span Test:			
– Forwards*	5.5±0.5	6.1±0.6	Ns
– Backwards*	5.2±0.4	5.3±0.5	Ns
Digit Symbol Test:			
– Raw score*	46.4±2.8	51.5±3.1	0.01
– Time to complete 3rd row	156.1±16.4	127.4±9.2	0.001
Quality of Life	17.4±1.1	17.3±1.2	Ns

\* Large score denotes better psychological functioning, in other cases smaller score denote worse psychological functioning. Ns – not significant (Means ± SD).

tively). Increase in IGF-1 concentration correlated significantly with  $T_3$  concentration ( $r=0.63$ ,  $p=0.005$ ). Improvement on POMS Vigor-Activity subscale correlated with increase in water body mass ( $r=0.71$ ,  $p=0.001$ ) and improvement on HAD depression subscale correlated with decrease in cortisol concentration ( $r=0.46$ ,  $p=0.06$ ). Increase in thyrotropin level correlated positively with improvement in mood on POMS Tension-Anxiety subscale ( $r=0.45$ ,  $p=0.06$ ) and with better performance on digit span test ( $r=0.53$ ,  $p=0.02$ ). However, it worsened copy time on digit symbol test ( $r=0.59$ ,  $p=0.01$ ). It should be mentioned that we found only seven statistically significant correlation among 140 calculated.

### Discussion

This study confirmed, that GH replacement in adult GH deficient patients improves mood and cognitive functioning, but not quality of life. Long-term studies, lasting for several years usually are used to show changes in quality of life (13, 14).

Improvement in mood and cognition paralleled changes in thyroid hormone concentration, IGF-1

concentration and changes in body composition. Improvement in mood was most evident on scales expressing confusion, vigor and fatigue, i. e. symptoms most frequently observed in GH deficient patients (15). Improvement in cognitive functioning was most evident on tests, reflecting incidental learning and psychomotor speed.

At least two mechanisms may be responsible for the improvement in psychological well-being after GH treatment. The first one is related to GH effects on body composition (16) and extracellular water volume (17). Strong and significant positive correlation between increase in vigor-activity subscale of POMS and water body mass supports hypothesis, proposed by T. Rosen et al. (17), that restoration of extracellular water may explain reduction of fatigue after GH replacement.

Besides, the study confirmed significant increase in lean body mass after long-term GH therapy (18, 19), but not decrease in fat body mass, as it was detected in other studies (20).

The other possible explanation of the positive GH effect on mood is based on findings demonstrating possible direct central GH effects on the brain neuro-

transmitters and on thyroid hormone concentration. Our study had replicated data indicating that GH treatment causes increase in  $T_3$  concentration and decrease in  $T_4$  level (21). Similar parallel changes in mood and thyroid hormone concentration are observed after different antidepressant treatment, such as antidepressive medication (22), lithium (23), electroconvulsive therapy (24), sleep deprivation (25) and light therapy (26) suggesting that serum decrease in  $T_4$  level and/or increase in  $T_3$  level is related to antidepressive effect. Similar effects on serum  $T_4$  and  $T_3$  concentration paralleling improvement in mood and cognition were demonstrated in a study comparing thyroid replacement with  $T_4$  monotherapy to  $T_4$  and  $T_3$  combination (27–29).

In this study we found that improvement in mood

after GH treatment was directly related to increase in IGF-1 concentration. Strong positive correlation between change in IGF-1 concentration and  $T_3$  concentration was demonstrated, suggesting importance of  $T_3$  and -IGF-1 interaction in psychological well-being.

In summary, this study demonstrates that improvement in psychological functioning after GH replacement in GH deficient adult patients may be related to multiple endocrine changes as well as to changes in body composition.

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## **Augimo hormono stokojančių suaugusių pacientų psichologinės funkcijos po pakaitinio gydymo augimo hormonu: ryšys su endokrinine sistema ir kūno kompozicija**

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**Raktažodžiai:** augimo hormonas, augimo hormono stoka, emocinė būklė, pažintinės funkcijos, gyvenimo kokybė.

**Santrauka.** Pakaitinis gydymas augimo hormonu gerina suaugusiųjų, stokojančių augimo hormono, psichologinę būklę ir gyvenimo kokybę. Tyrimo tikslas. Nustatyti ryšius tarp emocinės būklės, pažintinių funkcijų, gyvenimo kokybės, kūno kompozicijos bei endokrininės sistemos pokyčių prieš gydymą ir praėjus 6 mėn. po pakaitinio gydymo rekombinantiniu augimo hormonu. Tyrime dalyvavo 18 suaugusiųjų, stokojančių augimo hormono, kuriems nustatytas augimo hormono stokos sindromas. Augimo hormoną pacientai vartojo po 12 IU per savaitę. Po 6 mėn. pakaitinio gydymo augimo hormonu statistiškai reikšmingai pagerėjo emocinės būklės rodikliai (nuotaikos profilio skalė, POMS) bei pažintinių funkcijų testų rodikliai. Gyvenimo kokybės pokyčiai nebuvo statistiškai reikšmingi. Po augimo hormono terapijos reikšmingai padidėjo pirmojo insulinoaugimo faktoriaus (IGF-1) bei trijodtironino koncentracijos kraujyje, o laisvojo tiroksino koncentracija reikšmingai sumažėjo palyginti su jų koncentracijomis iki gydymo. Kortizolio, tirotropino, augimo hormono koncentracijos kraujyje pokyčiai nebuvo statistiškai reikšmingi. POMS skalės suminio rodiklio bei judrumo-aktyvumo subskalės rodiklio pokyčiai koreliavo su kūno vandens masės padidėjimu, o HAD depresijos rodiklio sumažėjimas – su kortizolio koncentracijos sumažėjimu.

Tyrimo duomenimis, pakaitinis gydymas augimo hormonu gerina suaugusiųjų, stokojančių augimo hormono, emocinę būklę ir pažintines funkcijas. Šis pagerėjimas susijęs su kūno vandens masės bei endokrininės sistemos pokyčiais.

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