Alterations in thyroid hormone levels following growth hormone replacement exert complex biological effects.

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INTRODUCTION

Alterations in the hypothalamic-pituitary-thyroid axis have been reported following growth hormone (GH) replacement, with a decline in circulating T4 concentration the most consistent finding.

However, the clinical significance of GH-induced alterations in circulating levels of thyroid hormone is unclear.

Concentration of other certain serum proteins and lipoproteins are influenced by minor changes in thyroid status. In addition, resting energy expenditure (REE) and systolic time intervals on echocardiography are very sensitive to circulating thyroid hormone levels.

AIM

Examine the relationship between changes in serum concentration of thyroid hormones and known biological markers of thyroid hormone action following GH supplementation.

PATIENTS & METHODS

We performed a prospective, observational study of adult hypopituitary patients receiving GH replacement as part of routine clinical care.

Subjects with and without TSH deficiency were included. Other hormones were adequately replaced prior to growth hormone treatment as per standard clinical practice.

Baseline tests performed before GH supplementation –

- Thyroid function tests, IGF-1, and basal pituitary blood tests.
- Serum markers of thyroid hormone action including ferritin, sex hormone binding globulin (SHBG), creatinine kinase (CK) and lipoproteins.
- REE was measured using a ventilated calorimeter and systolic time intervals were assessed by transthoracic echocardiogram.

GH dose was titrated to achieve an IGF-1 in the upper half of age-related reference range

Tests were repeated after a 3-6 months on a stable dose of GH.

REFERENCES

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RESULTS

20 male hypopituitary patients were studied before and after GH replacement.

Baseline characteristics are outlined in Table 1.

Male/Female	20/0	
Aetiology of GHD (%)		
• NFPA	10 (50)	
• Prolactinoma	4 (20)	
• Other	6 (30)	
MPHD (%)	17 (85)	
On Thyroxine (%)	13 (65)	
	Median	Range
Age (years)	52.5	(21.8-68.6)
BMI (kg/m2)	31.34	(19.2-49.7)
GH dose (mg/day)	0.34	(0.15-0.5)

Table 1. Baseline demographic features.

MPHD Multiple Pituitary Hormone Deficiencies. GHD Growth Hormone Deficiency

Body mass index(BMI) did not change during the study.

Following growth hormone replacement, IGF-1 levels rose significantly +114.4±12.3µg/L, p<0.0001.

FreeT4 levels declined as expected (-1.28±0.44pmol/L, p=0.02). Reverse T3 levels also fell (-3.44±1.42ng/dL; p=0.03) and freeT3 levels increased significantly (+0.34±0.15pmol/L; p=0.03).

REE did not rise as expected with GH substitution. Also, cardiac systolic time intervals were unchanged

Alterations in serum biomarkers of thyroid hormone action are shown in Table 2. Significant alterations in ferritin, Cu and caeruloplasmin concentrations were more closely correlated with changes in serum freeT4 rather than IGF-1.

Serum biomarker of TH action	Pre-GH Mean (SEM)	Post-GH Mean (SEM)	CI; p value
Ferritin ng/ml	87.98 (15.01)	61.09 (12.75)	-39 to -3.4 p=0.005*
CK U/L	154.8 (26.77)	149.5(18.81)	-25.00 to 11.00 p= 0.6809
SHBG nmol/L	35.85(4.263)	34.09(4.117)	-5.960 to 2.430 p= 0.3895
Copper umol/L	16.99(0.8815)	15.26(0.7878)	-3.089 to -0.3855 p= 0.0152*
Caeruloplasmin g/L	0.2540(0.01229)	0.2305(0.01325)	-0.0451 to -0.00184 p= 0.0356*

Table 2. Impact of GH replacement on serum biomarkers of thyroid hormone (TH) action.

Lipid Fraction mg/dL	Pre-GH Mean (SEM)	Post-GH Mean (SEM)	CI; p value
Tot. Chol	192.6(11.58)	191.3(9.875)	-15.24 to 12.61 p= 0.8435
LDL	105.1(7.798)	104.3(6.945)	-9.855 to 8.355 p=0.8630
HDL	44.44(2.208)	45.06(1.707)	-2.382 to 3.632 p=0.6641
Large HDL	9.500(1.351)	11.25(1.149)	0.2746 to 3.225 p=0.0232*
Intermediate HDL	25.5(1.201)	25.5(0.908)	-1.348 to 1.348 p> 0.9999
Small HDL	9.375(0.978)	8.188(0.634)	-3.005 to 0.6296 p=0.1840
Lp (a) nmol/L	46.64(11.40)	62.08(15.65)	0.0 to 25.50 p=0.0034*

Table 3. Alterations in lipid parameters following GH substitution in tandem with alteration in thyroid hormone levels. Data presented for patient s with MPHD only (n=17)

The effect of GH substitution on lipid parameters is shown in Table 3. The metabolic effects of GH substitution and thyroid hormone fluctuations were most marked in patients with multiple pituitary hormone deficiency (MPHD).

DISCUSSION

The interaction between GH and the thyroid axis can have a major implications for patients who commence GH therapy, particularly as the diagnosis of central hypothyroidism (CH) relies mainly on circulating free T4 levels[1]. This is complicated by the fact that a free T4 concentration within the population reference range does not exclude CH and the performance of free T4 assays varies considerably, particularly at the lower end of the reference range.

As demonstrated in our study, free T4 levels decline with the GH replacement. However, the biological and clinical significance of this is unclear in the face of rising a freeT3 level. Our data demonstrate that ferritin, Cu and caeruloplasmin declined significantly following GH supplementation, suggesting reduced hepatic exposure to thyroid hormone.

The improvement in REE with GH replacement, reported by other investigators, was not observed in our study[2]. This may have been due to declining tissue exposure to thyroid hormone.

Complex alterations in lipid profile, including a rise in large HDL particles and Lp (a) may have been attributable to alteration in exposure to thyroid or growth hormone, or both.

We conclude that growth hormone replacement does not improve the biological actions of thyroid hormone in adults hypopituitary patients.

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