Cardiac status after long-term growth hormone replacement therapy in adult growth hormone deficient patients.

A single centre audit based on echocardiographic investigations before and during GH replacement therapy

Sissela Skoglund[1], Ulla Feldt-Rasmussen[1], Marianne Klose[1] and Christian Hassager[2]

[1]Department of Medical Endocrinology, Rigshospitalet, University Hospital of Copenhagen, Denmark

[2]Department of Cardiology, University Hospital of Copenhagen, Denmark

Background and aim

Growth hormone (GH) is known as a hormone involved in regulation and influence of somatic growth but also of a long variety of metabolic pathways. GH exerts its effect in the body directly and indirectly, by stimulating insulin like growth factor-1 (IGF-1) production. Both GH and IGF-1 receptors are expressed in cardiac myocytes.

GH deficiency may develop deformities of cardiac structure as well as impaired systolic and diastolic functions. Further, earlier investigations indicate that IGF-1 excess has an hypertrophic effect on cardiac cells.

The aim of this study was to determine the effects of long-term GH treatment on heart anatomy and function among adult GH deficient patients.

Patients and methods

All GH deficient patients followed at Rigshospitalet with available echocardiography data at treatment baseline, 3-5 years and 8-10 years follow up were included. 25 naïve GH deficient patients i.e. patients who had never received GH therapy before, and 16 semi-naive patients i.e. patients previously on GH substitution therapy, but who had not received GH within 6 months before baseline evaluation.

Ultrasonic and biochemical data were collected retrospectively. Echocardiographic assessments were performed in accordance with the recommendations of the American Society of Echocardiography with focus on left ventricular structure and function.

Results

Table 1. Baseline characteristics of N = 41 GH deficient patients. Results are expressed as N (%) or mean ± standard error of the mean if normally distributed, and otherwise as median (range).

Baseline characteristics	N (%)
Gender	
- Female	16 (39)
- Male	25 (61)
Growth hormone deficiency onset	
- Adult-onset	23 (56)
- Childhood-onset	18 (44)
Growth hormone therapy	
- Naive	25 (61)
- Semi-naive	16 (39)
Etiology of pituitary disease	
- Craniopharyngioma	3 (7)
- Secreting pituitary adenoma	3 (7)
- Nonfunctioning pituitary adenoma	9 (22)
- Other extrasellar tumors	10 (25)
- Cranial irradiation due to malignancy outside the cranium	1 (2)
- Idiopathic	1 (2)
- Other	14 (35)
IGF-I SDS	-0.95 ± 0.3
Height, cm	171.9 ± 1.8
Weight, kg	80.9 ± 2.6
Body mass index, kg/m2	27.3 ± 0.7
Body surface area, m^2	1.9 ± 0.0
Systolic blood pressure, mmHg	120 ± 3
Diastolic blood pressure, mmHg	77 ± 2
Total cholesterol, mmol/L	4.9 ± 0.2
LDL, mmol/L	3.2 ± 0.2
HDL, mmol/L	1.3 ± 0.1
Triglycerides, mmol/L	1.0 (0.3 - 6.4)
Serum Testosterone, mmol/L (men, N= 25)	17.5 ± 2.2
Other hormonal deficiency	
- Gonadal axis	25 (61)
- Thyroid axis	29 (71)
- Hypothalamic-pituitary-adrenal axis	20 (49)
- Antidiuretic hormone axis	7 (17)

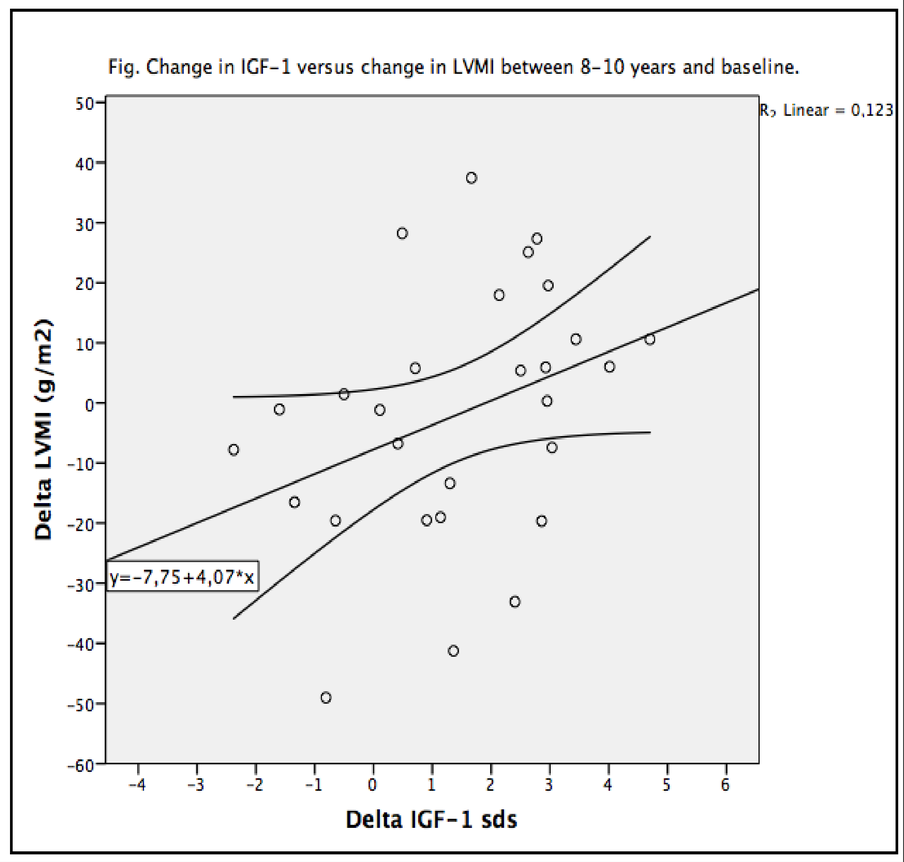
Table 2. IGF-1 standard deviation scores at follow-up compared to baseline in different groups. All numbers are expressed as mean ± standard error of the mean. Results are generated from a mixed model analysis. * P<0.05

IGF-1 standard deviation scores	N	Baseline	3-5 years	8-10 years
All patients	41	- 0.9 ± 0.3	1.0* ± 0.4	0.5* ± 0.3
Adulthood-onset total	23	- 1.48 ± 0.29	1.0* ± 0.4	0.3* ± 0.4
Childhood-onset total	18	- 0.27 ± 0.43	0.9 ± 0.6	0.7* ± 0.5
Men	25	- 0.9 ± 0.3	1.4* ± 0.5	0.9* ± 0.3
Women	16	- 1.0 ± 0.5	0.4* ± 0.5	- 0.0 ± 0.5
Naive	25	-1.4 ± 0.3	1.0* ± 0.4	0.4* ± 0.4
Semi-naive	16	-0.3 ± 0.4	0.8 ± 0.6	0.6 ± 0.5

Table 3. Left heart dimensions (A), systolic function (B) and diastolic function (C) at follow-up compared to baseline of N= 41 patients. Results are expressed as mean ± standard deviation. Measurements from echocardiography. Results generated by a mixed model analysis. *P <0.05.

A. Cardiac structure	Baseline	3-5 years	8-10 years
Inter ventricular septum diameter (mm)	9.1 ± 2.1	9.2 ±2.2	9.1 ± 2.0
Left ventricular internal dimension end diastole (mm)	45.7 ± 8.5	46.8 ± 7.8	45.6 ± 8.8
Left ventricular internal diameter end systole (mm)	29.5 ± 5.0	30.9 ± 5.9	26.8 ± 6.2
Left ventricular posterior wall dimension (mm)	8.9 ± 1.7	9.4 ± 1.8	9.0 ± 1.6
Left ventricular mass (g)	145.6 ± 51.1	151.4 ± 52.9	141.6 ± 48.5
Left ventricular mass index (g/m2)	74.1 ± 20.5	76.6 ± 21.3	72.7 ± 20.4
B. Systolic function			
Fractional shortening (%)	37.1 ± 8.9	34.0 ± 9.0	40.3 ± 12.5
C. Diastolic function			
Mitral valve flow E/A ratio	1.4 ± 0.6	1.3 ± 0.5	1.3 ± 0.5
Mitral valve deceleration time (s)	0.19 ± 0.07	0.19 ± 0.04	0.19 ± 0.05

Figure 1. Change in IGF-1 SDS versus change in Left Ventricular Mass Index between 8-10 years and baseline. Fitted line and 95 % confidence interval are shown.: P=0.068. y= -7.75+4.07*x



- No significant difference was observed in cardiac structure, nor in cardiac systolic or diastolic function during long term GH therapy.
- When dividing the patient cohort into subgroups a decrease in diastolic function was observed among naïve and adulthood-onset patients.
- A non-significant positive correlation was observed between change in IGF-1 SDS versus change in LVMI, at 3-5 years and 8-10 years follow-up.

Conclusions

Results from this study indicate that treatment duration of 8-10 years with GH replacement therapy in physiological doses in GH deficient patients appears not to be harmful, considering cardiac status. Verification of a positive effect of GH replacement on left ventricular mass index will, however, require a larger cohort of GHD patients.