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Summary

OBJECTIVES To assess effects of GH replacement therapy on cardiac structure and function, exercise capacity as well as serum lipids in elderly patients with GH deficiency (GHD).

PATIENTS AND METHODS Thirty-one patients (six females, 25 males), aged 60–79 years (mean 68 years) with GHD on stable cortisone and thyroxine substitution were studied. All men with gonadotropin deficiency had testosterone and one woman had oestrogen replacement. They were randomized in a double-blind manner to GH or placebo treatment for 6 months, followed by another 12 months GH (Humatrope, Eli Lilly & Co, Uppsala, Sweden). GH dose was 0·017 mg/kg/week for 1 month and then 0·033 mg/kg/week divided into daily subcutaneous injections at bedtime. Echocardiography, exercise capacity tests and serum lipid measurements were performed at 0, 6, 12 and 18 months.

RESULTS During the 6-month placebo-controlled period there were no significant changes in the placebo group, but in the GH-treated group there was a significant increase in IGF-I to normal levels for age, with median IGF-I from 6·9 to 18·5 nmol/l, increase in resting heart rate and maximal working capacity. During the open GH study, IGF-I increased from 8·7 to 19·2 nmol/l at 6 months and 18·8 nmol/l at 12 months ($P \leq 0\cdot001$). At 6 months, in the open GH study group, a minor decrease in aortic outflow tract integral (VTI) from 21·8 to 20·7 cm ($P = 0\cdot031$) and an increase in heart rate at rest from 63 to 67 bpm ($P = 0\cdot017$), heart rate at maximum exercise from 138 to 144 bpm ($P = 0\cdot005$) and maximum load at exercise from 142 to 151 Watts ($P = 0\cdot014$) were seen. These changes were temporary and returned at 12 months with no significant difference from baseline values. Left ventricular dimensions and blood pressure showed no significant changes. At 6 months, in the open GH study group, there was a significant decrease in serum low-density lipoprotein (LDL) cholesterol from 3·7 to 3·4 mmol/l ($P = 0\cdot006$), a decrease in LDL/HDL ratio from 3·4 to 3·1 ($P = 0\cdot036$) and a decrease in serum total cholesterol from 5·6 to 5·3 mmol/l ($P = 0\cdot036$). At 12 months, serum lipids showed same changes with a significant decrease in serum LDL cholesterol ($P = 0\cdot0008$), in LDL/HDL ratio ($P = 0\cdot0005$) and in serum total cholesterol ($P = 0\cdot049$). Serum HDL cholesterol showed no significant change at 6 months, at 12 months a significant increase was seen from 1·2 to 1·4 mmol/l ($P = 0\cdot007$). There were no significant changes in serum triglycerides.

CONCLUSIONS GH substitution to elderly patients with GHD caused only a transient increase in heart rate. At the end of the 12 months there were no significant changes on cardiac noninvasive structural and functional parameters. Maximal working capacity transiently improved. Thus, the therapy was safe without negative effects on cardiac structural and functional noninvasive parameters. Lipid profiles improved with reduction of serum LDL cholesterol accompanied by significant improvement of LDL/HDL ratio and serum HDL cholesterol after 12 months treatment.

In adulthood, GH still plays important physiological roles through anabolic and lipolytic actions as well as maintenance of cardiac performance. GH deficiency (GHD) of childhood-onset is associated with reduced left ventricular mass and systolic and diastolic function (Amato *et al*., 1993; Merola *et al*., 1993; Cittadini *et al*., 1994; Thuesen *et al*., 1994; Valcavi *et al*., 1995; Fazio *et al*., 1997; Sartorio *et al*., 1997). This is still inconsistent

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in adult-onset GHD. Evaluation of GH replacement therapy in supraphysiological doses in clinical trials has shown an improvement of the left ventricular mass and the systolic function (Cuneo *et al.*, 1991; Caidahl *et al.*, 1994; Johansson *et al.*, 1996a; Ter Maaten *et al.*, 1999), and also diastolic function in young and middle-aged patients with GHD of childhood-onset (Valcavi *et al.*, 1995). GHD is also associated with higher serum cholesterol, low-density lipoprotein (LDL) cholesterol (DeBoer *et al.*, 1994; Vahl *et al.*, 1998) and triglycerides (Vahl *et al.*, 1998) compared with healthy subjects. GH replacement therapy in clinical trials has shown improvement in serum cholesterol (Attanasio *et al.*, 1997; Cuneo *et al.*, 1998; Vahl *et al.*, 1998) and LDL cholesterol (Cuneo *et al.*, 1998).

It is well known that patients with hypopituitarism on stable hormone replacement therapy but without GH therapy have higher mortality and morbidity from cardiovascular causes (Rosén & Bengtsson, 1990; Bulow *et al.*, 1997). Several risk factors were linked to this increase in cardiovascular mortality such as hyperlipidaemia, truncal obesity and hypertension (Rosén *et al.*, 1993).

In spite of low GH secretion in old age, there was a significant reduction of spontaneous GH secretion and impaired GH response to arginine when patients with pituitary diseases were compared with age-matched healthy elderly subjects (Toogood *et al.*, 1996), raising the possibility of benefit from GH therapy in elderly patients with GHD. This is supported by a study that showed an impaired cardiac performance in elderly patients with GHD (Colao *et al.*, 1999). We have previously shown that a low GH dose increasing serum IGF-I to levels within the normal range for age can be given without significant side-effects (Fernholm *et al.*, 2000).

In this present study, we evaluate the effect of 6 months placebo-controlled and 12 months open GH therapy in physiological doses to elderly patients with GHD on cardiac structure and function, exercise capacity and serum lipids.

Patients and methods

Patients

Thirty-one patients aged 60–79 years (mean 68 years), six females and 25 males, with adult-onset pituitary disease with a known duration of 0·5–40 years, participated (Table 1). They were treated at three centres in Sweden: Department of Endocrinology, University Hospital, Malmö; Department of Endocrinology and Diabetology, Karolinska Hospital, Stockholm; and Department of Medicine, Norrland's University Hospital, Umeå. Informed consent was obtained from each patient and the study was approved by the regional Ethics Committees and by the Swedish Medical Product Agency. The majority had panhypopituitarism due to a pituitary tumour and its treatment. The diag-

Table 1 Characteristics of 31 elderly patients with GHD

Number of subjects	31
Males/females	25/6
Age, years mean (range)	68 (60–79)
BMI kg/m^2, mean (range)	25·5 (19·3–29·7)
IGF-I SD, mean (range)	−3·01 (−8·07–(−0·02))
Panhypopituitarism, *n*	23
Nonsecreting adenoma, *n*	24
Prolactinoma, *n*	1
Idiopathic, *n*	2
Pituitary cyst, *n*	1
Empty sella syndrome, *n*	1
Post encephalitis, *n*	1
Craniopharyngioma, *n*	1

nosis of GHD was based on an insufficient response to a standard GH provocation test with arginine (*n* = 29) or insulin (*n* = 2). All patients fulfilled the consensus criterion for severe GHD, i.e. a maximal peak GH response less than 9·0 mU/l (Growth Hormone Research Society, 1998). The mean maximal GH concentration was 0·9 ± 0·3 mU/l. All patients had serum IGF-I levels below mean for 70-year-old healthy subjects. Thirty patients were ACTH-deficient and 24 patients were TSH-deficient. These patients received adequate and stable replacement therapy for ACTH (cortisone acetate) and TSH deficiencies for at least 6 months. None had received GH replacement previously. All the males with LH/FSH deficiency (*n* = 22) had testosterone replacement and one woman had systemic treatment with conjugated oestrogens. The patients had normal fasting blood glucose and no history of diabetes mellitus. One patient had evidence of impaired arterial circulation in the legs with intermittent claudication. Apart from their pituitary insufficiency, the patients suffered from no other serious illness and were living independently. Four patients had well-controlled benign hypertension.

Study design and protocol

During the first 6 months of the study, the patients were randomized in a double-blind and parallel fashion to inject either biosynthetic human GH (Humatrope®, Eli Lilly Sweden AB, Uppsala, Sweden) or placebo as a subcutaneous (s.c.) single daily injection at bedtime. The study was then continued unblinded, with GH treatment for another 12 months. The starting dose was 0·017 mg/kg/week in the first month of treatment and then increased to 0·033 mg/kg/week for another 5 months. Thereafter, i.e. 6 months after the start of the study, all patients were again treated with 0·017 mg/kg/week for 4 weeks to avoid breaking the blind protocol and then with 0·033 mg/kg/week for 11 months. The total daily GH dose had a range from 0·25 to 0·40 mg (mean 0·3 ± 0·07 mg). The doses of thyroxine, cortisone acetate and gonadal steroids were kept constant during the study. The study

was performed on an outpatient basis and blood samples were drawn in the morning after an overnight fasting.

At the start of the study and every 6 months, a physical examination including blood pressure, heart rate and side-effects were registered and blood samples were collected for measurement of IGF-I and serum lipids. Echocardiography and exercise tests were also performed at the start and thereafter every 6 months.

As a result of the randomization procedure 15 patients (one female, 14 males) constituted the group to receive 18 months of active GH treatment and 16 patients (five females, 11 males) the group to receive placebo for 6 months followed by 12 months of active GH treatment. At inclusion there were no difference between the groups regarding age (mean 67·8 *vs.* 68·6 years), body mass index (BMI; 25·3 *vs.* 25·7 kg/m^2) or aetiology of pituitary insufficiency (with 13 patients having pituitary adenomas in the GH group and 12 in the placebo group). Panhypopituitarism was found in 12 and 11 patients, respectively. Twenty-eight patients completed the whole study period. The patient who had history of intermittent claudication stopped treatment after 10 months due to vascular surgery of arterial insufficiency in a leg, which led subsequently to amputation. One patient withdrew without stating the reason after 15 months and one patient did not take her GH injections the last month. All these three patients received placebo in the first 6 months and had active treatment thereafter. Thus, regarding the data analysis, all patients were included during first 6 months placebo controlled period (15 patients receiving GH treatment and 16 patients receiving placebo). The effect of GH was then evaluated in the combined group of 28 patients receiving GH treatment for at least 12 months. In the placebo group, the visit at 6 months was considered as comparable to the visit at start in the GH group.

Biochemical methods

Serum IGF-I was determined by radioimmunoassay (RIA) as described by Bang *et al*. (1991); to minimize interference of remaining IGFBPs in the extract. The detection limit was 1 nmol/l, and the intra- and interassay coefficients of variation (CV) were 4% and 11%. Normal range of IGF-I, which declines by age, was established in 448 healthy subjects aged 20–96 years (Hilding *et al*., 1999). The geometrical mean concentration at 20 years of age was 29·7 nmol/l (range 20·8–62·9 nmol/l), at 65 years of age 17·6 nmol/l (10·2–30·7 nmol/l) and at 75 years of age the mean was 15·0 nmol/l (8·6–26·1 nmol/l). The IGF-I-values were also expressed as SD scores calculated from the regression line of values in these subjects.

Serum total cholesterol, high-density lipoprotein (HDL) and triglycerides were analysed by routine methods at the Departments of Clinical Chemistry at each investigating centre. LDL cholesterol concentrations were calculated according to the formula suggested by Friedewald *et al*. (1972).

Echocardiography evaluations

Transthoracic echocardiography was performed according to a standardized protocol used at all investigating centres. M mode measurements were performed according to the recommendations by the American Society of Echocardiography (Sahn *et al*., 1978). These measurements were used to determine left atrial and ventricular dimensions, as well as the ventricular wall thickness. Atrio-ventricular (AV) plane motion was measured to determine global cardiac function and presented as a mean of four positions as described by Alam & Höglund (1992). Percentage of fractional shortening was calculated as the difference between left ventricular diastolic and systolic internal dimensions divided by the left ventricular internal diastolic dimension. EF slope (diastolic closing motion of the mitral valve leaflets) was also measured. Aortic outflow tract integral (velocity time integral = VTI), which is the area under the velocity *vs.* time plot taken at aorta valve and provides a measure of valvular flow and hence of the systolic function, was measured from apical position. Flow velocities by pulsed Doppler examinations were recorded. Rapid filling wave (peak flow velocity in early diastole, E wave) and atrial filling wave (peak flow velocity in atrial contraction, A wave) were measured and the E/A ratio, a measure of the diastolic function, was calculated as a measure of atrial contribution to the left ventricular filling in diastole. Pulmonary vein systolic wave (S wave) and diastolic wave (D wave) were measured also and S/D ratio was calculated, a measure of the diastolic function. One single investigator at each centre made all echocardiography examinations.

Exercise tests

ECG at rest was recorded before and every minute during the the test. Exercise capacity was measured by bicycle exercise test (ergonometry) and was recorded as maximal workload (Watt). The test was started at a workload of 50 Watts, increased by 20 Watt/min in Malmö. In Stockholm and Umeå, the test was started at 30 Watts for women and 50 Watt for men and then increased by 10 Watt/min for both sexes until symptoms of exhaustion or the test was interrupted for safety reasons. Blood pressure and heart rate were monitored before and at maximum workload.

Statistical evaluation

The descriptive values are presented as mean and range. Results are presented as median and range during the placebo controlled period and as mean ± SEM in the open study. In the first 6-month placebo-controlled period, to compare between the GH group and the placebo group regarding changes in parameters, Mann–Whitney *U*-test was used. Differences between baseline values and values at 6 months within the group were assessed by Wilcoxon

signed rank test. The results from the first 6-month placebo-controlled period are presented separately.

To assess the effects of GH treatment compared with baseline in the 12-month open GH period one-way repeated measures analysis of variance (ANOVA) was used followed by Wilcoxon signed rank test. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using StatView software (version 4·5 for Window, Abacus Concept Inc., Berkeley CA; SAS Institute, Inc., Cary, NC, USA).

Results

Serum IGF-I

At baseline, all the patients had IGF-I levels below the normal mean for age and 2/3 below −2SD. Basal IGF-I did not differ in the placebo and GH group. During the placebo-controlled first 6 months of the study there was no change in the mean level of IGF-I in the placebo group. In the GH-treated group there was a significant rise in IGF-I ($P < 0.001$) from 6·9 nmol/l (3·1–13·5 nmol/l) to 18·5 nmol/l (10·4 – 32·8 nmol/l). With the two groups combined, IGF-I increased during 12 months of treatment, to levels normal for age, from 8·7 ± 0·7 nmol/l to 19·2 ± 1·5 nmol/l at 6 months and 18·8 ± 1·6 nmol/l at 12 months (Fig. 1). Subnormal IGF-I levels for age at 12 months were found in three patients, of whom one was female.

Echocardiography studies

During the first 6 months of the study there were no differences from baseline values within placebo group or between groups.
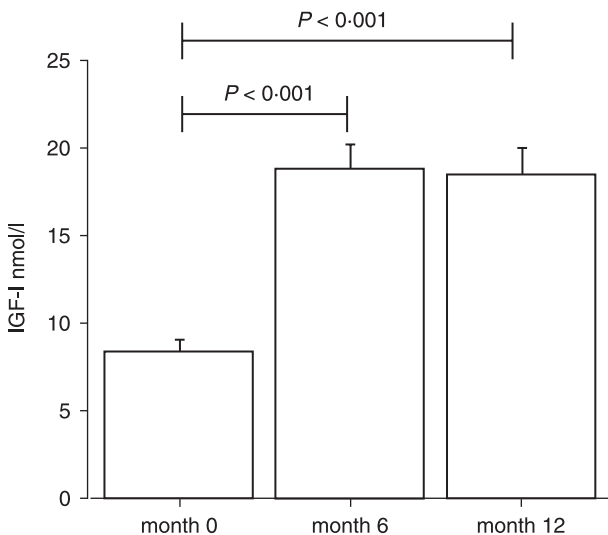

Fig. 1 Concentrations of serum IGF-I at baseline, after 6 and 12 months ($n = 28$) of GH replacement in patients aged 60–79 years with GHD. Values are given as mean ± SEM.
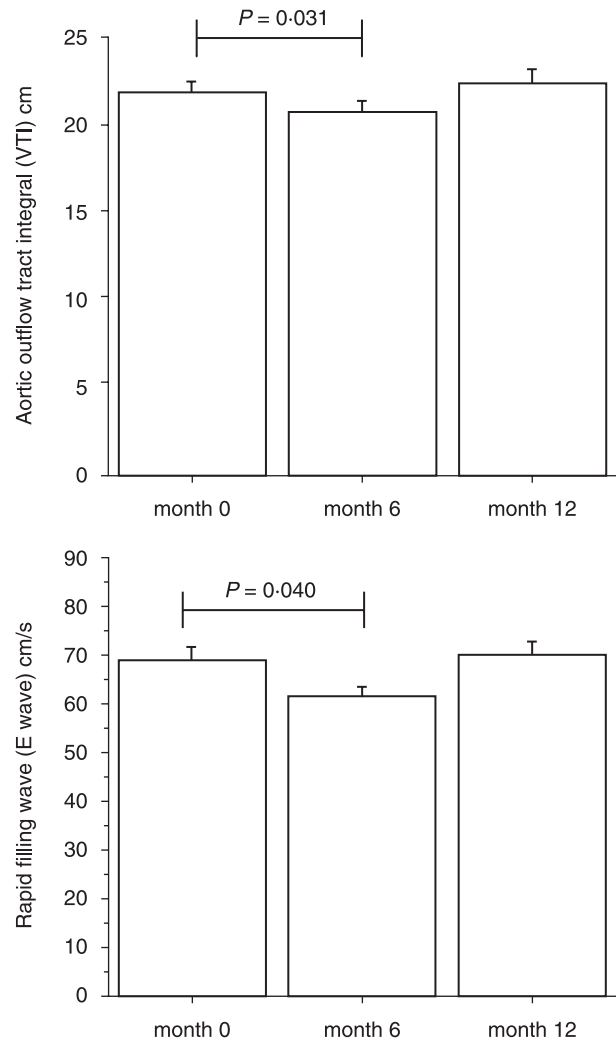

Fig. 2 Aortic outflow tract integral (VTI) and rapid filling wave (E wave) at baseline, after 6 and 12 months ($n = 28$) of GH replacement in patients aged 60 – 79 years with GHD. Values are given as mean ± SEM.

In the combined group, regarding the systolic function, there was a minor ($P = 0.0314$) reduction in aortic outflow tract integral (VTI), from 21·8 ± 0·7 cm at baseline to 20·7 ± 0·8 cm at 6 months (Fig. 2). This change returned at 12 months, with no difference from values at start. A transient decrease in rapid filling wave (E wave) was seen at 6 months from 69 ± 3 cm/s to 62 ± 2 cm/s ($P = 0.040$; Fig. 2), at 12 months it returned with no difference from baseline. No significant changes were seen in fractional shortening, AV plane movement or EF slope (Table 3).

Concerning diastolic function no significant changes were seen in the E/A ratio (rapid filling wave/atrial filling wave) or S/D ratio (pulmonary vein systolic wave/pulmonary vein diastolic wave). A tendency to reduction in E/A ratio was noticed at

Table 2 Effects of GH replacement therapy on cardiac parameters in GH-deficient elderly patients during a 6-month placebo-controlled period

	Placebo			GH		
	Basal	Month 6	*P* basal *vs* month 6	Basal	Month 6	*P* basal *vs* month 6
VTI, cm	21 (13–31)	20 (14–28)	NS	22 (17–28)	22 (14–27)	NS
AV-plane movement, mm	12·7 (8·9–15·2)	12·5 (7–16·7)	NS	12·6 (10–15·3)	12·2 (10–14)	NS
Fractional shortening percentage	35 (26–48)	36 (14–47·5)	NS	34 (15·6–45)	38 (20·5–48)	NS
EF slope, mm/s^2	281 (161–1060)	296 (192–684)	NS	250 (152–492)	167 (176–492)	NS
E wave, cm/s	66 (47–117)	71 (48–120)	NS	64 (44–86)	60 (45–80)	NS
E/A ratio	0·9 (0·6–1·2)	0·9 (0·7–1·5)	NS	0·9 (0·6–1·5)	0·8 (0·7–1·8)	NS
S/D ratio	1·4 (0·9–1·7)	1·3 (0·7–1·6)	NS	1·6 (1–2·4)	1·4 (1·1–1·8)	NS
LVIDd, mm	50 (40–62)	51 (40–61)	NS	50 (41–62)	50 (42–62)	NS
LVIDs, mm	31 (21–45)	34 (25–49)	NS	34 (25–42)	33 (26–44)	NS
Posterior wall dimension, mm	9 (7–13)	11 (6–13)	NS	11 (7–15)	11 (7–15)	NS
Septum dimension, mm	11·2 (9–15·6)	11 (9–14·4)	NS	11·6 (7–14·2)	11·3 (7–14·5)	NS
Left atrial dimension, mm	37 (29–48)	36 (27–48)	NS	38 (31–45)	38 (32–44)	NS
Heart rate at rest, bpm	70 (47–102)	66 (45–110)	NS	58 (48–75)	67 (50–86)	0·029
Heart rate at max exercise, bpm	147 (112–179)	138 (113–177)	NS	142 (102–162)	148 (107–160)	0·05
Max work load, Watts	129 (70–210)	140 (80–120)	NS	150 (105–180)	160 (110–210)	0·012

VTI, aorta outflow tract integral; EF slope, the diastolic closing motion of the mitral valve leaflets; E wave, rapid filling wave; E/A ratio, rapid filling wave/atrial filling wave; S/D ratio, pulmonary vein systolic wave/pulmonary vein diastolic wave; LVIDd and LVIDs, left ventricular interior diameter at diastole and systole, respectively. Values are given as median and range.

6 months from 1·0 ± 0·04 to 0·9 ± 0·05 and returned at 12 months to 1·0 ± 0·05 due to the decrease in E wave (Table 3). When males and females were separated, males showed the significant decrease in the aortic outflow tract integral and rapid filling wave as well as increase in heart rate.

Left ventricular interior diameter at systole (LVIDs) and diastole (LVIDd), septum dimension, posterior wall dimension and left atrium dimension showed no significant changes during 12 months of GH treatment (Table 3).

Exercise test, heart rate and blood pressure

At baseline there was no difference between the placebo and GH group. In the placebo group controlled period, no differences were seen in the placebo group. Within the GH-treated group, there was an increase in heart rate at rest from 58 bpm (48– 75 bpm) at start to 67 bpm (50–86 bpm) at 6 months (*P* = 0·029), and a borderline increase in heart rate at maximal work capacity at 6 months from 142 bpm (102–162 bpm) to 148 bpm (107– 160 bpm; *P* = 0·050). Maximum work capacity also showed significant increase (Table 2) after 6 months from 150 Watts (105–180 Watts) to 160 Watts (110–210 Watts; *P* = 0·012).

In the open GH period a significant increase in heart rate at rest was seen from 63 ± 2 bpm at start to 67 ± 2 bpm at 6 months (*P* = 0·017). At 12 months there was no difference from start values. A similar change was seen in heart rate at maximal workload, i.e. an increase from 138 ± 3 bpm to 144 ± 3 bpm at 6 months

(*P* = 0·005). This increase returned at 12 months with no significant difference from values at start (Fig. 3). Maximal work capacity also showed a temporary improvement from a mean 142 ± 6 Watts to a mean 151 ± 7 Watts at 6 months (*P* = 0·014) which returned at 12 months with no difference to the baseline values. Maximal work capacity and IGF-I-values were correlated positively at 6 months with *r* = 0·488 (*P* = 0·015) but not at 12 months with *r* = 0·318 (*P* = 0·14).

No significant changes were seen in the diastolic or systolic blood pressure either at rest or at maximum workload (Table 3).

Serum lipids measurements

Basal and after the first 6 months of the treatment period there were no differences in serum cholesterol, LDL cholesterol, HDL cholesterol, triglycerides or LDL/HDL ratio between the GH and placebo groups. In the GH group, after 6 months, there was a significant reduction in serum cholesterol (*P* = 0·013) from 5·7 to 5·2 mmol/l, a significant reduction in serum LDL cholesterol (*P* = 0·013) from 3·9 to 3·3 mmol/l and in LDL/HDL ratio (*P* = 0·016) from 3·7 to 3·0. In the placebo group, after 6 months, there was also a significant reduction in serum cholesterol (*P* = 0·02) from 5·8 to 5·5 mmol/l, a significant reduction in serum LDL cholesterol (*P* = 0·014) from 4·0 to 3·6 mmol/l and in LDL/HDL ratio (*P* = 0·008) from 3·8 to 3·1.

In the combined group, at 6 months, there was a significant reduction in serum total cholesterol (*P* = 0·036) from 5·6 to

Table 3 The effects on cardiac parameters of GH replacement for 12 months to GH-deficient elderly patients

	Basal	Month 6	P basal *vs.* month 6	Month12	P basal *vs.* month 12	ANOVA
AV plane movement, mm	12·5 ± 4	12·3 ± 0·3	NS	12·2 ± 0·3	Ns	NS
Fractional shortening percentage	33 ± 2	36 ± 2	NS	41 ± 3	Ns	NS
EF slope, mm/s^2	313 ± 23	291 ± 14	NS	325 ± 18	Ns	NS
E/A ratio	1 ± 0·04	0·9 ± 0·05	NS	1 ± 0·05	Ns	NS
S/D ratio	1·4 ± 0·07	1·4 ± 0·06	NS	1·4 ± 0·08	Ns	NS
LVIDd, mm	50 ± 1	50 ± 1	NS	50 ± 1	Ns	NS
LVIDs, mm	33 ± 1	31 ± 1	NS	32 ± 1	Ns	NS
Posterior wall dimension, mm	10 ± 0·3	10 ± 0·3	NS	11 ± 0·3	Ns	NS
Septum dimension, mm	11 ± 0·3	12 ± 0·3	NS	12 ± 0·3	Ns	NS
Left atrial dimension, mm	37 ± 1	37 ± 1	NS	36 ± 1	Ns	NS
Max work load, Watts	142 ± 6	151 ± 7	0·014	150 ± 8	Ns	0·017
Diastolic BP at rest, mmHg	84 ± 2	83 ± 2	NS	85 ± 2	Ns	NS
Systolic BP at rest, mmHg	147 ± 4	148 ± 4	NS	148 ± 4	Ns	NS
Systolic BP at max workload, mmHg	212 ± 6	218 ± 5	NS	215 ± 5	Ns	NS

E/A ratio, rapid filling wave/atrial filling wave ration; S/D ratio, pulmonary vein systolic wave/pulmonary vein diastolic wave ratio; LVIDd and LVIDs, left ventricular interior diameter at diastole and systole, respectively. Values are given as mean ± SEM.

5·3 mmol/l, a decrease in serum LDL cholesterol ($P = 0·006$) from 3·7 to 3·4 mmol/l and in LDL/HDL ratio ($P = 0·036$) from 3·4 to 3·1. At 12 months there was a significant reduction in serum total cholesterol ($P = 0·049$) from 5·6 to 5·4 mmol/l, a significant reduction in serum LDL cholesterol ($P = 0·0008$) from 3·7 to 3·3 mmol/l (Fig. 4) and in LDL/HDL ratio ($P = 0·0005$) from 3·4 to 2·7. Serum HDL cholesterol showed no change at 6 months, at 12 months there was a significant increase ($P = 0·007$) from 1·2 to 1·4 mmol/l. Serum triglycerides showed no significant changes.

Discussion

This study is, to our knowledge, the first study performed in this age group of patients with GHD to assess the effects of a very low dose of GH on cardiac parameters and serum lipids.

As mentioned initially, this study was designed to assess the effects of 12 months of GH replacement. One unexpected finding was the temporary decrease of aortic outflow tract integral (velocity time integral or VTI) and rapid filling wave (E wave) at 6 months. This can indicate a minor reduction in the cardiac function, although in the open study phase, fractional shortening and AV plane movement, reflecting systolic function, were unaffected. This is in contrast with previous studies which demonstrated an improvement in LV function (Cuneo *et al.*, 1991; Amato *et al.*, 1993; Beshyah *et al.*, 1994; Caidahl *et al.*, 1994; Thuesen *et al.*, 1994; Valcavi *et al.*, 1995; Christiansen *et al.*, 1996; Fazio *et al.*, 1996). The decrease in VTI can be a consequence to the decrease in E wave. The mechanism of this reduction in VTI and E wave is unknown. One explanation may be the lower doses of GH used compared with the supraphysi-

ological doses used in previous studies as well as the age of the patients in this study (Alam & Höglund, 1992; Amato *et al.*, 1993; Barton *et al.*, 1993; Caidahl *et al.*, 1994; Thuesen *et al.*, 1994; Christiansen *et al.*, 1996; Hoffman *et al.*, 1996). Most previous studies were performed in adults (< 60 years) with or without childhood-onset GHD (Cittadini *et al.*, 1994; Thuesen *et al.*, 1994; Christiansen *et al.*, 1996; Cuocolo *et al.*, 1996; Fazio *et al.*, 1997; Sartorio *et al.*, 1997). Those patients, as compared to matched controls, had decreased ventricular mass as well as systolic and diastolic function, which improved during GH replacement using rather high doses of GH. In patients with adulthood-onset of GHD, normal left ventricular mass, wall thickness and systolic and diastolic functions were found at rest, but after physical exercise there was a decreased increase in peak ejection fraction in patients with nearly the same age group as in the present study using the equilibrium radionuclide angiography (Colao *et al.*, 1999). Thus, when GHD appears in childhood the normal development of the heart is impaired, while the cardiac function does not seem to deteriorate when GHD appears in adulthood.

In consistence with most of the studies in GHD patients, there was a significant increase in heart rate at rest as well as at exercise (Jörgensen *et al.*, 1989; Caidahl *et al.*, 1994; Thuesen *et al.*, 1994; Valcalvi *et al.*, 1995; Christiansen *et al.*, 1996; Hoffman *et al.*, 1996). This increase in heart rate might be a compensatory mechanism against the reduction in aortic outflow tract integral (VTI) and E wave to maintain the cardiac output. Supporting evidence to this explanation is that the increase in heart rate was also temporary and returned to baseline values at 12 months as VTI and E wave did. Explanations given previously to the increase in heart rate do not apply here. First, the direct inotropic
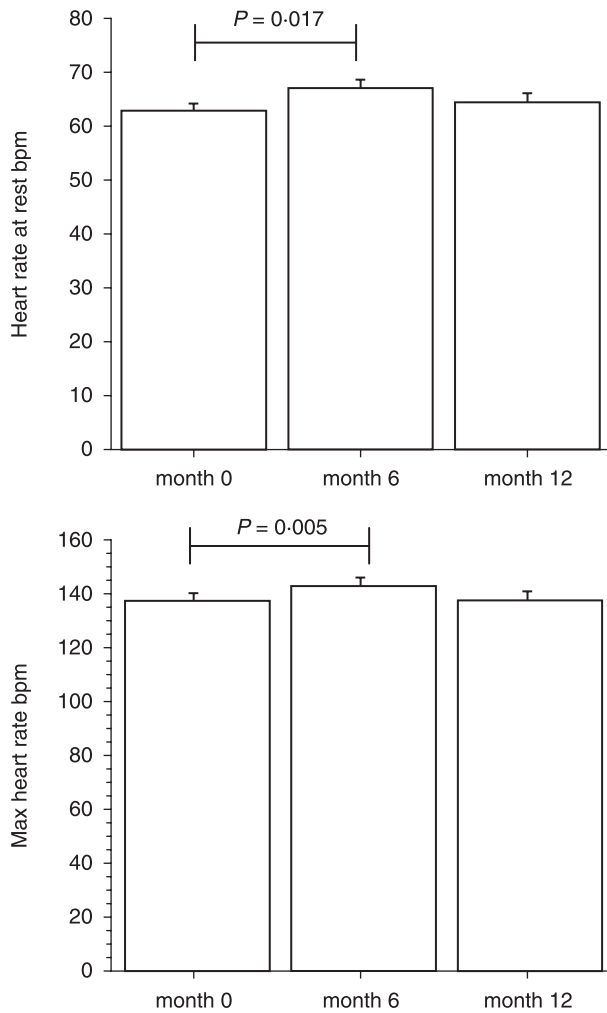
Fig. 3 Heart rate at rest and at max. workload at baseline, after 6 and 12 months ($n = 28$) of GH replacement in patients aged 60–79 years with GHD. Values are given as mean ± SEM.
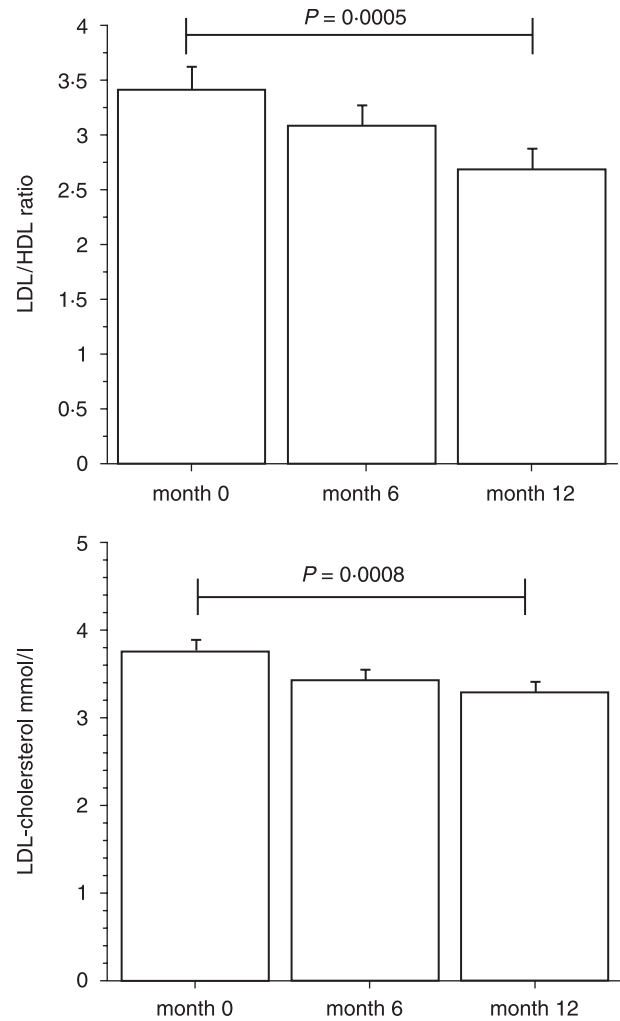

Fig. 4 Concentrations of serum LDL cholesterol and LDL/HDL ratio at baseline, after 6 and 12 months ($n = 28$) of GH replacement in patients aged 60−79 years with GHD. Values are given as mean ± SEM.

effect of GH is unclear as fractional shortening was unchanged; in contrast, a reduction in VTI occurred. Second, a possible reduction in peripheral vascular resistance is difficult to prove here as neither the diastolic and systolic blood pressures showed any changes. Third, an effect of fluid retention is also unlikely because the left ventricular internal diameters at diastole and systole showed no significant changes.

When women were excluded and men in the open GH study were analysed separately, there was a decrease in aortic outflow tract integral and rapid filling wave (E wave) as well as an increase in heart rate. The same dose of GH per kg body weight was given to women and men. It is known from the previous studies (Johansson *et al*., 1996b; Burman *et al*., 1997; Fernholm *et al*., 2000) that females are less sensitive to GH replacement

therapy than males, for instance, concerning the effect on bone metabolism and body composition.

In our study as in the majority of the other studies (Jörgensen *et al*., 1989; Amato *et al*., 1993; Barton *et al*., 1993; Beshyah *et al*., 1994; Thuesen *et al*., 1994; Nass *et al*., 1995; Hoffman *et al*., 1996), there were no significant changes in the systolic and diastolic blood pressure during GH replacement. This finding was even proven in one study (Christiansen *et al*., 1996) during 5 years GH replacement. Thus, it seems to be there is no risk for hypertension to elderly patients on GH replacement. One study on childhood-onset GHD (Cittadini *et al*., 1994) has shown a significant increase in systolic blood pressure but diastolic blood pressure was unchanged.

In short-term studies in young patients, GH replacement for 8 weeks and 6 months improved exercise capacity (Cuneo *et al*.,

1991; Orme *et al.*, 1992; Beshyah *et al.*, 1994; Caidahl *et al.*, 1994; Cittadini *et al.*, 1994; Nass *et al.*, 1995). In long-term placebo-controlled studies (Whitehead *et al.*, 1992; Jörgensen *et al.*, 1994) and one open study (Jörgensen *et al.*, 1996), using higher doses of GH, there were improvement in physical performance. In our open study, a temporary improvement in exercise capacity was seen. However, a correlation between IGF-I and exercise capacity at 6 months may indicate a temporary effect of IGF-I on exercise capacity in this age group, probably due to improvement in well being, muscle mass and increase heart rate.

The reduction in serum LDL cholesterol and LDL/HDL ratio during GH replacement is consistent with most of the studies (Brosnan *et al.*, 1993; Rusell-Jones *et al.*, 1994; Beshyah *et al.*, 1995; Cuneo *et al.*, 1998). The upregulation of hepatic LDL receptors by a direct effect of GH is suggested to cause the decrease in LDL cholesterol (Fig. 4). This was seen *in vitro* as well as clinically (Rudling *et al.*, 1992; Angelin *et al.*, 1993). An indirect effect of GH is also suggested to decrease LDL cholesterol through inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-Co A reductase) activity with a subsequent reduction of mevalonic acid which is a precursor in cholesterol synthesis (Russell-Jones *et al.*, 1994). This later explanation seems to be applicable to our findings. A significant decrease in serum cholesterol could be seen as in almost all previous studies (Brosnan *et al.*, 1993; Russell-Jones *et al.*, 1994; Beshyah *et al.*, 1995; Attanasio *et al.*, 1997; Cuneo *et al.*, 1998; Vahl *et al.*, 1998; Gillberg *et al.* 2001).

Serum triglycerides were unchanged during GH therapy in our study as in all other studies (Brosnan *et al.*, 1993; Russell-Jones *et al.*, 1994; Beshyah *et al.*, 1995; Attanasio *et al.*, 1997; Cuneo *et al.*, 1998; Vahl *et al.*, 1998).

With the GH doses used, 0·25–0·40 mg/day, serum IGF-I concentrations obtained were largely within the age-related normal range. It seems appropriate to administer a GH dose leading to IGF-I levels that do not exceed the upper physiological age-related range. The side-effects with this dose were few, mainly attributed to fluid retention and subsided spontaneously or following minor reduction of the GH dose. Two patients who had normal glucose tolerance test at start showed a deterioration of glucose tolerance (Fernholm *et al.*, 2000).

In conclusion, GH replacement to elderly patients with GHD for 12 months in physiological doses leading to improved IGF-I levels within the age related physiological range seems to be safe and without negative effects on cardiac structural or functional non invasive parameters. It seems also to have beneficial effects on lipid profile. The side-effects were few and mild.

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