Long-term growth hormone (GH) replacement of adult GH deficiency (GHD) benefits the heart

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Abstract

Objective: Growth hormone (GH) deficiency is related to increased cardiovascular mortality. We studied clinical status, concentration of amino-terminal-pro B-type natriuretic-peptide (NT-proBNP) and echocardiographic parameters during long-term GH replacement (GH-R).

Methods: Fifty-one patients (29 females), 45.9 ± 11.3 years (mean ± s.d.), median follow-up 36.2 months, echocardiography and laboratory determinations initially and at 12-months intervals.

Results: At the last follow-up (last observation carried forward) (LFU (LOCF)) insulin-like growth-factor-1 standard deviation score (IGF-1 SDS) was ±1 in 92% of the patients. The median NT-proBNP declined significantly and stabilized (~40.5%) at LFU (LOCF) due to patients with a basal NT-proBNP >125 ng/L (indicative of heart failure). The basal NT-proBNP and the final IGF-1 SDS were significant predictors of the NT-proBNP at LFU (LOCF). Initially left ventricular enddiastolic diameter (LVEDD), left ventricular posterior wall diameter (LVPWD) and ejection fraction (EF) were normal, while interventricular septum diameter (IVSD) and left ventricular mass index (LVMi) were slightly increased. LVPWD and IVSD had significantly declined by year three. The LVMi was moderately to severely abnormal in 37.3 and 52.0% of patients initially and at LFU (LOCF). At LFU (LOCF) LVMi and IGF-1 were significantly correlated in the 14 male patients of this subgroup.

Conclusion: Long-term GH-R of GHD positively affected ISVD and LVPWD. In a subgroup of patients with severe GHD, LVMi increased concomitantly to the decline in NT-proBNP and this was positively correlated to the final IGF-1 concentration. Whether this observation indicates a positive development in a structurally altered heart muscle (reversal of adverse remodelling) or poses a future risk for heart failure needs further follow-up.

Introduction

Long-term observations of GH-deficient patients suggest a causal relationship of GH deficiency (GHD) and increased cardiovascular mortality (1, 2, 3, 4, 5). In adult-, as well as childhood-onset GHD, adverse cardiac remodelling consisting of structural and functional muscular changes that is reduced left ventricular mass and cardiac output have been described (6). In addition, GHD is associated with early atherosclerotic lesions (6, 7), due to the presence of several cardiovascular risk factors that is unfavourable lipid profile and parameters of oxidative stress (8), insulin resistance (1, 9), increased fibrinogen concentration, plasminogen activator inhibitor-1 activity (10) and increased sympathetic nervous activity (6). Several studies reported an increase in intima media diameter, as well as pathologic vascular compliance (1, 7, 9) in patients with GHD. Furthermore, GHD, as part of the multiple hormonal deficiency syndrome of chronic heart failure (CHF) is related to impaired functional cardiac
capacity, left ventricular remodelling and increased all-cause mortality (4, 5).

GH replacement therapy (GH-R) has been reported to have a positive impact on cardiovascular functionality, while its effects on mortality are still a matter of debate (11, 12).

Suspected heart failure is evaluated by either echocardiography and/or the determination of NT-proBNP. M-mode-echocardiography is used to diagnose heart failure. An important parameter for left ventricular (LV) function is the ejection fraction (EF), while left ventricular mass (LVM) is a risk factor and predictor of cardiovascular events (13). NT-proBNP is an amino-terminal fragment of proBNP. The concentration of BNP is regulated by the cardiac volume or pressure load and BNP is released from the cardiac muscle cells in response to increased wall-stretch and volume overload (14, 15, 16, 17, 18). In a population of primary care patients suspected of CHF, a plasma concentration >125 ng/L specifically indicates CHF. The application of an age-adjusted cut-off value for NT-proBNP (<75 years and ≥75 years: >125 ng/L and >450 ng/L, respectively) does not increase the diagnostic performance (16). Continuously high plasma concentrations of NT-proBNP correlate with an increased cardiovascular mortality (19). Echocardiographic parameters indicative for heart failure correlate well with the NT-proBNP plasma concentration as has been shown for different populations, that is, general community (18, 20), patients with diabetes mellitus (21), hypertension and coronary artery disease (22). In conclusion, the predictive value of NT-proBNP for systolic heart failure is well established (15, 16, 17, 20, 23, 24) and NT-proBNP with a cut-off >125 ng/L is a biomarker for heart failure according to the European Society of Cardiology (25).

**GH replacement therapy in GHD**

GH-R improved several echocardiographic or magnetic resonance imaging (MRI) endpoints like LVEDD, stroke volume (26), left ventricular mass (LVM), left ventricular mass index (LVMi) (27, 28, 29, 30), ejection fraction (EF) (27) as well as cardiac index at rest and in response to exercise (31). In patients with CHF and GHD, GH-R improved exercise capacity, vascular reactivity, LV function (32) and delayed the progression of CHF during a 4-year period (12).

The concentration of NT-proBNP in GHD has been shown to be either normal or pathologically increased (33, 34, 35), and unaffected or reduced during GH replacement (32, 33, 34, 35).

Taken together, data on the cardiovascular effect of GH-R as represented by either echocardiography and/or the NT-proBNP concentration are inconsistent. Published data on the cardiac effect of GH-R refer to small groups of patients, between 5 and 28 patients or short-term effects – 6–12 months (26, 27, 28, 29, 30, 31, 36). Those with a longer observation period (48–60 months) included only a small number of patients (n = 14 for both) (12, 37). These studies used different echocardiographic parameters and the effect on NT-proBNP has been inconclusive.

However, it probably takes more time for a demonstrable GH effect on cardiovascular risk factors (lipid, glucose metabolism and body fat distribution) and cardiac musculature. So far, no data are available on the time course of the impact of GH-R on cardiac parameters over several years.

We therefore prospectively investigated the effect of long-term GH-R on cardiovascular outcome as determined by clinical status, NT-proBNP and echocardiography before and at annual intervals in 51 patients with GHD of various aetiologies. The primary endpoint of the study was a decline of the NT-proBNP concentration during GH replacement. As secondary endpoints we expected (i) a negative correlation between the IGF-1 and NT-proBNP concentration before and during GH replacement and (ii) a correlation between the echocardiographic parameters and NT-proBNP before and during GH-R, as well as an improvement of echocardiographic parameters during GH-R.

**Methods**

GH-deficient patients were included as they presented at the outpatient clinic and consented to participate. At this time point, basal data were collected. GHD was diagnosed by the determination of the insulin-like growth-factor-1 (IGF-1) concentration and either insulin-induced hypoglycaemia (IHG) or GHRH-arginine test, whenever IHG was contraindicated. Definition of GHD required an IGF-1 concentration below 2 SDS of the age-adjusted median IGF-1 concentration and a GH increase during either insulin-induced hypoglycaemia (blood glucose concentration below 40 mg/dL and signs and symptoms of hypoglycaemia) to less than 3 µg/L or during the GHRH-arginine-test to less than 11 µg/L, 8 µg/L and 4 µg/L for those with a BMI below 25 kg/m², between 25–30 kg/m² or above 30 kg/m², respectively.

IHG was performed with 0.1–0.2 IU insulin/kg bodyweight. The GHRH-arginine test consisted of 0.5 g arginine-hydrochloride/kg bodyweight and 1 µg GHRH/kg
bodyweight intravenously. Blood was drawn for the determination of glucose, GH and cortisol during IHG and GH during GHRH-arginine-test at 0, 15, 30, 45, 60, 90 and 120 minutes. An LHRH-TRH-test was used for the determination of gonadal and secondary thyroid insufficiency. LHRH 100µg and TRH 200µg (both Ferring, Kiel, Germany) were injected intravenously. LH, FSH, PRL and TSH were determined at 0, 15, 30, 45 and 60 minutes in addition to basal free T4 in all patients, testosterone in men and oestrogen in premenopausal women. All hormonal determinations were performed by Labor Berlin (Berlin, Germany) as a routine clinical service. The diagnosis of GHD and the initiation of GH replacement therapy were in accordance with the suggestions of the German Endocrine Society (11, 38, 39, 40). Patients were included if their age was >18 and <75 years and were willing to comply with regular study visits. Exclusion criteria were an underlying heart failure due to reasons other than GHD, contraindications to GH therapy, severe hepatic (transaminases >3 times of upper limit of normal (ULN)) or kidney (GFR <30mL/min) failure, any malignant disease and pregnancy in women.

**Laboratory investigations**

IGF-1 (Chemiluminescence assay, IDS-iSYS, Frankfurt, Germany) with age-adjusted normal values, sensitivity and specificity were 1.9µg/L and 100%, respectively, intra- and interassay coefficients of variation were 1–7% over the whole spectrum of concentrations. NT-proBNP (Electro-Chemiluminescence Immuno-assay; Roche) with age-adjusted normal values, sensitivity was 5 ng/L, intra- and interassay coefficients of variation were <6.1% (41, 42). A concentration >125 ng/L is considered indicative for heart failure (25). All determinations were performed in duplicate and the mean of both determinations was used as the final result.

**Replacement therapy (RT) for pituitary insufficiency**

Forty-four patients (44/51, 86.3%) received RT for at least one pituitary hormone deficiency: hydrocortisone – 39 patients (76.5%), sex-hormone (oestrogen or testosterone) – 18 patients (35.3%; female 4/29, 13.8%, male 14/22, 63.6%) and thyroid hormone (t-triiodothyronine) – 29 patients (56.9%). Taken together, seven patients were without any hormonal RT, twelve patients had at least one, twenty-two patients had two and ten patients had three stable hormonal RT before initiation of GH-R. Thyroid hormone RT, adjusted as necessary, resulted in normal thyroxin concentrations throughout.

GHD was diagnosed after surgery of a pituitary adenoma (31/51, 61%), macro- (23/51, 45.1%), micro-adenoma (8/51, 15.7%). Endocrine inactive tumours comprised 21 of 23 macroadenomas and 5 of 8 microadenomas that is 26 of 31 adenomas (83.9%). Two and three macroadenomas and microadenomas were prolactinomas (5/31, 16.1%). Other aetiologies were traumatic brain injury or subarachnoidal haemorrhage (5/51, 9.8%), germinoma, hypophysitis or empty sella syndrome, three patients each (n=9, 3/51, 5.9%, each), childhood-onset of GHD (2/51, 3.9%) and spongioblastoma, a suprasellar dermoid cyst, secondary haemochromatosis due to β-thalassemia or Sheehan syndrome (n=4, 1/51, 1.9% each).

**Cardiovascular disease**

Cardiovascular disease at baseline was diagnosed in 19 (37.3%) patients: Arterial hypertension in 12 (12/19, 63.2%), mitral insufficiency in 6 (6/19, 31.6%), aortic valve replacement in one patient (1/19, 5.3%), respectively. Thirteen of these patients (13/19, 68.4%) were on cardiovascular medication (β-blocking agents: n=3, Ca antagonist: n=1, ACE inhibitor: n=3, angiotensin receptor antagonist: n=1 or a combination of these with thiazide in two patients, n=5). The doses of the cardiovascular medication had been stable for at least 3 months before the study. Thus, 47 (92.2%) patients were on some kind of medication that is hormonal RT other than GH and/or cardiovascular medication and only four patients (7.8%) were without any medication before initiation of the GH-R.

Before the initiation of GH-R, the diagnosis of GHD was confirmed in all patients as indicated earlier. GH-R was initiated with 0.1 (median, 0.1–0.2) mg/day subcutaneously at night with a constant injection site throughout the investigation at either the abdomen or the anterior thigh, according to the patient’s preference. Initially all patients were seen at regular, short intervals for dose adjustment of GH replacement. GH replacement was titrated (increase/decrease by 0.1 mg steps) to achieve an age-adjusted IGF-1 concentration within the range of the median IGF-1 ± 1 SDS. Thereafter follow-up investigations were scheduled every 6 months for re-evaluation and eventual adjustment of the GH dose. One investigator (UP) performed all dose adjustments. No patient reported side effects of GH therapy. A variability of 20% of the IGF-1 concentration was considered acceptable before the dose was adjusted. Each dose adjustment was controlled.
within 6 weeks. Follow-up investigations were performed within 12 ± 1, 24 ± 1 and 36 ± 1 months on therapy.

Echocardiography was performed by dedicated cardiologists from the department of Cardiology, Charité, CVK, who were unaware of the status of the patient (treated or untreated). Complete M-mode and 2D analyses were performed using an ultrasound mechanical system (GE Healthcare, Modell Vivid 7 und E9) equipped with a 3.5 MHz transducer, according to the standardization recommended for cardiac chamber quantification by echocardiography in adults by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (13).

The following M-mode data were collected via a left parasternal route: LVEDD, normal values: 41–46 mm and 50–55 mm; IVSD, 7–10 mm and 8–11 mm; EF, 50–70%; female and male patients respectively. The LVM was calculated according to the Penn-Cube method: LVM = 1.04 × (LVEDD + LVPW + IVS)³ − LVEDD³ − 13.6 g. Normal LVM is 121 ± 40 g and 174 ± 45 g, females and males, respectively (43). LVM was standardized for body surface area (BSA) and reported as LVM Index (LVMI). BSA was calculated according to DuBois et al. BSA = 0.007184 × height (cm)⁰.⁷₂₅ × weight (kg)⁰.⁴₂₅ (44). LVMI mass was considered normal, mildly, moderately and severely abnormal within the indicated ranges: female 43–95, 96–108, 109–121, >122 g/m² and male 49–115, 116–131, 132–148, >149 g/m², respectively (13).

Statistical analysis

Data were calculated as mean ± s.d. or median (5–95th percentile) as appropriate. The Shapiro–Wilk W test was used in testing for normality. Percent values are given for (i) changes in concentrations, that is the percent decline, with the basal concentration set as 100% and (ii) to describe the number of patients achieving the therapeutic goal. There all patients that is 51, are set as 100%. We used the following statistical calculations: longitudinal comparisons were analysed by Friedmans test for nonparametric repeated measures of analysis of variance, the Wilcoxon’s paired-rank test for individual comparisons, with accounting for missing values by complete-case analysis. The evaluation of multiple parameters was performed by a general linear model. Correlations were calculated by Kendals Tau. A P < 0.05 was considered significant. For repeated calculations, the P level was corrected as indicated. Missing values were considered ‘missing completely at random’. To correct for missing values the last observation carried forward (LOCF) method was used for the last follow-up data, that is after the 3-year study period (n=5) and for the NT-proBNP concentration not determined by the laboratory due to unknown reasons at year 3 (n = 5). All data were calculated using Statistica 6 (StatSoft, Hamburg, Germany).

Ethical guidelines

This observational study was conducted in accordance with the ethical guidelines of GCP and the Helsinki Declaration of 1964, as revised in 2000 (45). The institutional Ethnic Committee of the Charité consented to the procedures and the publication of the data (EA2/089/159). All patients gave informed written consent to the use of their pseudonymized clinical data for scientific analysis and the publication of these data.

Results

Patient characteristics

Fifty-one patients were studied (Fig. 1). For details on patients’ characteristics refer to Table 1. No significant changes were observed for these parameters during the investigation. Clinical signs of overt heart failure (dyspnoea upon exertion (i.e. NYHA classification III and...

![Figure 1](https://eje.bioscientifica.com)

Flowchart. *Missing data, at year 3, five NT-proBNP determinations were not performed by the laboratory due to reasons unknown.
Table 1  Patients (n=51) characteristics at baseline.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± s.d.</th>
<th>Median, 5th–95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.9 ± 11.3</td>
<td>32.2, 5.0–220.1</td>
</tr>
<tr>
<td>Male (n = 22, years)</td>
<td>44.4 ± 12.2</td>
<td></td>
</tr>
<tr>
<td>Female (n = 29, years)</td>
<td>47.1 ± 10.6</td>
<td></td>
</tr>
<tr>
<td>Interval diagnosis to GH-R (months)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.3 ± 10.4</td>
<td>81.0, 56.0–119.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.5 ± 10.9</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>28.1 ± 5.3</td>
<td></td>
</tr>
<tr>
<td>Body surface area (BSA) (m²)</td>
<td>1.95 ± 0.3</td>
<td></td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124.8 ± 14.7</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.5 ± 10.9</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75.4 ± 11.0</td>
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</table>
*BMI, body mass index, normal: 18.5–25, overweight: 25–30, obesity: >30 (55).

IV), peripheral oedema) were not observed – neither at baseline nor during follow-up.

GH replacement therapy

GH-R was initiated with 0.1 mg/day (0.1–0.2) (median, 5th–95th percentile), subcutaneously, increased to 0.3 mg/day (0.1–0.8 and 0.1–1.1) at months 12 (n=51) and 24 (n=48), respectively and stabilized at 0.2 mg/day (0.1–1.2 and 0.1–1.2) at months 36 (n=46) or LFU (LOCF) (n=51). Forty-six (90%) patients completed 36 months of GH-R, median follow-up at the LFU (LOCF) (n=51) was 36.2 (13–55) months. Fourteen patients were investigated beyond the scheduled 36 months with a median follow-up of 52 (42–94) months.

IGF-1 concentration

The basal and follow-up median IGF-1 concentrations, as well as the qualitative IGF-range given as SDS for the age-adjusted median value are indicated in Table 2. GH-R significantly increased both parameters at all timepoints.

The pre-defined therapeutic aim for GH replacement was achieved at all time points, as indicated by the median IGF-1 SD score. In detail, after 1 year on therapy 69% (35/51) achieved the therapeutic goal, while 14% (7/51) and 18% (9/51) were below or higher, respectively. At years 2 and 3, the percentage improved to 71% (34/48) and 74% (34/46) within, 8% (4/48) and 4% (2/46) below and 21% (10/48) and 21% (10/48) higher than 1 SDS, respectively. At the LFU (LOCF) 92% (47/51) achieved their therapeutic goal, with 6 and 2% (3/51 and 1/51) below or higher than 1 SDS for the age-adjusted IGF-1 concentration. Analysing the percentage of patients within the therapeutic goal for three different age groups (<50 years, 50–60 years and >60 years) or according to sex, yielded comparable results (data not given).

NT-proBNP concentration

The NT-proBNP concentration continuously declined during GH replacement with a significantly lower concentration at year 2 compared to basal and remained lower than the basal concentration at year 3 as well as at the LFU (Table 2). Throughout neither the NT-proBNP concentrations, nor the number of patients with NT-proBNP higher than 125 ng/L or higher than the individual age-adjusted normal value were significantly different between the sexes.

The basal NT-proBNP concentration correlated negatively with the basal IGF-1 concentration (τ = -0.2698, P < 0.05, Fig. 2), as well as with the IGF-1 SDS (τ = -0.2912, P < 0.05). This correlation persisted, when corrected for sex, age and BMI at inclusion (multiple R² = 0.2092, P = 0.0109; IGF-1 basal BETA = -0.3856, P = 0.0056, age at inclusion BETA = -0.2687, P = 0.0475; sex BETA = -0.1310, P = 0.3228). Thus, the lower the absolute or qualitative

Table 2  IGF1 concentration (µg/L, mean ± s.d.), IGF-1 SDS (median, 5th–95th percentile) and NT-proBNP (ng/L, median, 5th–95th percentile). Statistical differences over the time course for each time point were calculated by Wilcoxon’s paired sample test.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean IGF-1 ± s.d.</th>
<th>Median IGF-1 SDS</th>
<th>Median NT-proBNP</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal, n = 51</td>
<td>107.8 ± 41.7</td>
<td>-0.9 (–3.9 to 0.3)</td>
<td>70.0 (5.0–187.0)</td>
<td>0.0565</td>
</tr>
<tr>
<td>After 1 year, n = 51</td>
<td>166.8 ± 50.9*</td>
<td>0.3 (–1.6 to 1.8)*</td>
<td>56.0 (10.0–191.0)</td>
<td>0.0065</td>
</tr>
<tr>
<td>After 2 years, n = 48</td>
<td>171.7 ± 50.1*</td>
<td>0.4 (–1.4 to 1.6)*</td>
<td>45.5 (5.0–265.0)</td>
<td>0.0529</td>
</tr>
<tr>
<td>After 3 years, n = 46</td>
<td>168.5 ± 42.1*</td>
<td>0.6 (–0.9 to 1.8)*</td>
<td>52.0 (8.0–221.0)</td>
<td>0.0312</td>
</tr>
<tr>
<td>LFU (LOCF), n = 51</td>
<td>165.4 ± 45.7*</td>
<td>0.6 (–1.1 to 1.8)*</td>
<td>62.0 (7.0–194.0)</td>
<td></td>
</tr>
</tbody>
</table>

1IGF-1 SDS, age-adjusted standard deviation score of IGF-1. 2LFU (LOCF) last follow-up (last observation carried forward). *P < 0.00001, thus all significantly different from basal. **P values corrected for multiple comparisons: significant at 1 year vs basal P < 0.05; 2 years vs basal P < 0.025; 3 years vs basal P < 0.0125; LFU vs basal P < 0.0062, accordingly significant differences are marked by bold numbers.

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The basal NT-proBNP concentration correlates negatively with the basal IGF-1 concentration \((n = 51)\). — Regression line and 95th percentile; basal NT-proBNP concentration vs basal IGF-1 concentration: \(\tau = -0.2698, P < 0.05\).

IGF-1 value, indicating a more severe GH deficiency, the higher the NT-proBNP concentration.

Using the NT-proBNP concentration at LFU (LOCF) as the dependent variable in a model including sex, age, IGF-1 SDS and NT-proBNP at inclusion, as well as IGF-1 SDS at LFU (LOCF), the overall model was highly significant \((R^2 = 0.4864, P < 0.000003)\). The basal NT-proBNP concentration yielded a 65% contribution \((\text{BETA} = 0.653, P < 0.000001)\) and the IGF-1 SDS at LFU (LOCF) a negatively correlated 39% contribution \((\text{BETA} = -0.3892, P < 0.0006)\) for the prediction of the final NT-proBNP. Hence, the variables determining the final NT-proBNP concentration were primarily a low basal IGF-1 concentration, that is severe GHD, corresponding to a high basal NT-proBNP concentration and secondarily the negatively correlated, final IGF-1 SDS.

An NT-proBNP concentration higher than 125 ng/L is indicative of CHF. If only those 15 patients with a NT-proBNP concentration above the cut-off of >125 ng/L were considered, the yearly decline of the NT-proBNP concentration during GH RT was –35.5% \((n = 15, P = 0.011), –40.1\% \((n = 14, \text{non-significant}, P = 0.048), –40.5\% \((n = 9, P = 0.012)\) and -40.5\% \((n = 15, P = 0.002)\) for the years 1, 2, 3 and the last follow-up (LOCF), respectively. Thus, NT-proBNP declined continuously during the first 2 years and stabilized thereafter at -40.5\%. Accordingly, the percent of patients with an NT-proBNP concentration above 125 ng/L declined from 29.4% \((15/51)\) at baseline to 11.8% \((6/51)\) at the last follow-up (LOCF) \((\text{Fig. 3})\). Importantly, no significant change of the NT-proBNP concentration during GH replacement was seen in those patients with a normal NT-proBNP concentration that is <125 ng/L at baseline. Therefore, the observed decline of the NT-proBNP concentration during GH replacement was primarily due to those patients with initially increased NT-proBNP concentrations.

As normal values for the NT-proBNP concentration are age dependent, we analysed the data differentiating those with a NT-proBNP concentration above or within the age-adjusted normal range. This analysis resulted in a slightly higher percentage of patients with a decline of their pathologically increased basal NT-proBNP concentrations during GH-R compared to the patients grouped according to a basal concentration of NT-proBNP >125 ng/L \((\text{data not given})\).

NT-proBNP, either individually increased \((\text{Spearman’s } R = -0.141, \text{ns})\) or >125 ng/L \((\text{Spearman’s } R = 0.0523, \text{ns})\) did not correlate with the clinical diagnosis of cardiovascular disease at baseline.

**Echocardiography**

Table 3 gives the echocardiographic parameters basal and during GH replacement. As expected, all parameters of LV diameters were physiologically significantly different between female and male patients at each time point. Both, LVEDD and LVPWD were within the normal range and remained so during the observation period \((\text{Friedman test: } P = 0.3196 \text{ and } P = 0.0484, \text{respectively})\), with a small, yet significant decline of the LVPWD after 3 years \((P < 0.0106)\). The IVSD was slightly increased that is mildly abnormal before therapy, and remained so, despite a small, yet significant decline at year 3 \((P < 0.0035, \text{Table 3})\). The EF was normal throughout.

The overall LVMi, initially slightly increased for both women and men \((103.9 \text{ g/m}^2 \text{ and } 128.4 \text{ g/m}^2, \text{respectively})\), significantly decreased till the second year of GH replacement, only to increase again at year 3, and was comparable to the basal values at the last follow-up \((\text{LFU (LOCF)}\) \((\text{Fig. 4A and Table 3})\). When classifying the LVMi as normal and mildly abnormal vs moderately and severely abnormal, 37.3% of the patients had a moderately or severely abnormal LVMi before therapy. During therapy, this percentage decreased to a minimum of 22.9\% percent at year 2 and increased again to 52.0\% at the LFU (LOCF) \((\text{Fig. 4B})\). This effect was more pronounced in male compared to female patients.

Multiple regression analysis, including the IGF-1 concentration basal and at year 3 of GH-R, yielded both
IGF-1 concentrations as significant predictors for the LVMi at the last follow-up (LOCF) in those male patients with a moderately or severely abnormal LVMi (multiple $R^2 = 0.6524$, $P = 0.05$) with a regression coefficient for IGF1 basal and at year 3 of BETA = −0.7377, $P = 0.0119$ and BETA = 0.5782, $P = 0.0376$, respectively. Thus, the lower the basal IGF-1 and the higher the concentration at year 3, the higher the risk of GH RT to result in a pathologically increased LVMi. Interestingly this effect was restricted to male patients and failed to be significant for the 12 female patients with moderately to severely abnormal LVMi at the LFU (LOCF).

The median NT-proBNP concentration of this subgroup of patients with moderately to severely increased LVMi had non-significantly declined (basal vs last follow-up (LOCF): −51.1% in males ($n = 14$) and −36.9% in female patients ($n = 12$)), while no such decline was observed in those patients with normal or only slightly increased LVMi at the last follow-up (LOCF) (basal vs last follow-up (LOCF): male −8.3% ($n = 8$), female −3.2% ($n = 17$)).

The NT-proBNP concentration demonstrated a small, but significant negative correlation basal, after 3 years as well as at the last follow-up (LOCF) with the intraventricular septum diastolic diameter and the left ventricular posterior wall thickness (basal, year 3 and LFU (LOCF)) NT-proBNP vs IVSD: $τ = −0.210$, −0.273, −0.234, $P < 0.05$ and NT-proBNP vs LVPWD: $τ = −0.317$, −0.472, −0.332, $P < 0.05$, respectively). Thus, a low diameter of both the IVSDD and the LVPD correlated with a higher NT-proBNP concentration.

### Figure 3

Percent of patients with the NT-proBNP concentration above or below 125 ng/L before and during GH RT. --- NT-proBNP ≤125 ng/L (normal), — NT-proBNP > 125 ng/L (increased), LFU (LOCF), last follow-up (last observation carried forward).

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal ($n=51$)</th>
<th>1 year ($n=51$)</th>
<th>2 years ($n=48$)</th>
<th>3 years ($n=40$)</th>
<th>LFU (LOCF) ($n=51$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSD Mean</td>
<td>11.0±1.9</td>
<td>11.0±1.9</td>
<td>11.0±1.9</td>
<td>11.0±1.9</td>
<td>11.0±1.9</td>
</tr>
<tr>
<td>LVETD Mean</td>
<td>45.2±3.5</td>
<td>46.0±3.5</td>
<td>46.0±3.5</td>
<td>46.0±3.5</td>
<td>46.0±3.5</td>
</tr>
<tr>
<td>LVPWD Mean</td>
<td>46.2±3.5</td>
<td>45.8±3.5</td>
<td>45.8±3.5</td>
<td>45.8±3.5</td>
<td>45.8±3.5</td>
</tr>
<tr>
<td>EF Mean</td>
<td>50.3±5.5</td>
<td>50.7±5.5</td>
<td>50.7±5.5</td>
<td>50.7±5.5</td>
<td>50.7±5.5</td>
</tr>
<tr>
<td>LVMi Mean</td>
<td>30.3±2.7</td>
<td>29.1±2.7</td>
<td>29.1±2.7</td>
<td>29.1±2.7</td>
<td>29.1±2.7</td>
</tr>
<tr>
<td>NT-proBNP Mean</td>
<td>10.6±1.7</td>
<td>10.6±1.7</td>
<td>10.6±1.7</td>
<td>10.6±1.7</td>
<td>10.6±1.7</td>
</tr>
</tbody>
</table>

Values corrected for multiple comparisons, significant at year vs basal $P < 0.025$; **2 years vs basal $P < 0.0125$; ***3 years vs basal $P < 0.0062$, significant $P$ indicated by bold numbers.
Long-term GH therapy in GH deficiency

We analysed the long-term effect of GH-R in GHD on the cardiac clinical status, NT-proBNP concentration and echocardiographic parameters. Due to a standardized and structured procedure in titrating the GH dose, 92% of the patients achieved their individualized age-adjusted IGF-1-goal and only 6% had a therapeutic result still below their therapeutic goals. No side effects were reported possibly due to the very slow titration process and the careful adjustment of the doses. These are optimal results as compared with the literature. Previous reports rarely indicated the therapeutic goals for the IGF-1 concentration (12, 26, 28, 29, 30, 31, 32, 46). Only three publications (30, 36, 47) gave the mean achieved IGF-1 SDS or percentile of normal age-adjusted IGF-1 concentrations and none indicates the percentage of patients within this range. However, if the percentage of patients ‘normalized’ during GH-R is not indicated, the cardiological results may refer to patients with a broad range of treatment efficacy, some undertreated, others overtreated (28, 32). The optimal data set would therefore include (i) definition of a therapeutic goal using IGF-1 SDS and (ii) the percent of patients achieving this goal at each time point during long-term observations. To allow a generalization of the cardiological results, we used a therapeutic goal of least 75% of the patients achieving an age-adjusted IGF-1 SDS ≥ 1.

Clinical status

GHD, either due to pituitary GH deficiency or part of the multiple hormone deficiency syndrome in CHF indicates an increased risk for or of CHF, respectively (1, 2, 3, 4, 5, 11, 12). In the present study, signs of overt heart failure were absent at baseline and during follow-up. The percent of GHD patients with mitral insufficiency was comparable to the overall prevalence of 9.5% for mild mitral regurgitation in the population (48).

NT-proBNP

NT-proBNP is a screening tool for, and marker of systolic heart failure (14, 15, 16, 17, 18, 20, 23, 24, 25). An increased concentration of NT-proBNP with a subsequent decline during GH-R has been demonstrated in patients with GHD by some (34, 35) but not by others (33, 49). Before GH-R one-third of our patients demonstrated an increased concentration of NT-proBNP (> age-adjusted ULN) or a concentration above the recommended cut-
off, that is, above 125 ng/L (25) for heart failure. This in accordance with the data from two small studies with an increased NT-proBNP concentration in 42% (5/12) (34) and 60% (18/30) (35), respectively, before GH-R. Both report a decline of the NT-proBNP concentration during GH RT, but only Wallaschofski et al. (35) indicate that this decline was primarily due to those patients with initially increased NT-proBNP concentration, similar to our study. We extend these data, as NT-proBNP negatively and significantly correlated with the basal IGF-1 concentration. Interestingly, in the study of Andreasen et al. (33), although none of their patients had an increased baseline NT-proBNP concentrations, the basal NT-proBNP was inversely correlated with the IGF-1 concentration, as were the relative changes of the NT-proBNP and IGF-1 concentrations during therapy. In our patients as well, NT-proBNP tended to negatively correlate with the IGF-1 concentration throughout the long-term observation period. The lower the IGF-1 concentration or IGF-1 SDS, indicating a more severe GH deficiency, the higher the NT-proBNP concentration. No correlation between the concentrations of IGF-1 and NT-proBNP was observed by Gruson et al. (34) despite of 90% of his patients achieving a normal age-adjusted IGF-1 concentration during 6 or 12 months of GH-R. In contrast, the overall mean ± s.d. given for the IGF-1 SDS by Wallaschofski et al. (35) indicates that at least some of their patients had an IGF-1 SDS below –1 SD of the IGF-1 SDS and thus were probably insufficiently treated, as was the case with all patients of Andreasen et al. (33). Thus, the short treatment period, the small number and/or insufficiently treated patients of these studies may preclude a negative correlation between the IGF-1 and NT-proBNP concentration or the changes of both parameters.

Taken together, we demonstrated (i) an increased NT-proBNP concentration, persistently and inversely correlated with the IGF-1 concentration at baseline and during therapy and (ii) a significant decline of NT-proBNP with increasing IGF-1 during GH-R.

The continuous decline of NT-proBNP did not differ significantly between patients with or without cardiovascular disease. This unexpected observation can possibly be explained: (i) the definition of cardiovascular disease may have been too unspecific; (ii) all patients were effectively treated while on the respective medications, without indications of heart failure, (iii) GHD per se has an effect on cardiac muscle reflected by an increased, yet not necessarily pathologically increased NT-proBNP concentration. Thus, in GHD patients NT-proBNP may not only be related to clinically evident heart failure, but the degree of structural myocardial changes in all patients with GHD. The negative correlation of NT-proBNP with the IGF-1 concentration is an argument in favour of this hypothesis.

GH, in addition to its anabolic effects, inhibits natriuresis and results in higher sodium and water body content (50). A GH-R-related increase in extracellular volume is a consistent finding. The effect of GH-R on plasma volume is mostly dependent on the duration of the therapy, unchanged during short-term yet increased during long-term GH-R (50). Whether these volume changes affect the NT-proBNP concentration has not been investigated so far. NT-proBNP is increased in hyponatraemia after overconsumption of hypotonic fluids (51). However, GHD is not associated with hyponatraemia. Peripheral oedema observed earlier with GH-R, with relative high starting doses for adult patients, did not occur in our patients with an initial GH dose of 0.1–0.2 mg/day s.c.. It is therefore highly unlikely that the initially increased NT-proBNP and the decline during therapy in our patients was due to electrolyte disturbances.

**Echocardiography**

Echocardiographic parameters were normal (13) or only minimally increased before and remained unchanged or slightly, but significantly decreased during GH RT. Reported results in the literature revealed a multifaceted picture as indicated in Table 4. This may be due to the different parameters measured, the small number of patients included, the variable duration of GHD before substitution therapy, the short-term observation (mostly 12 months) and the therapeutic goals of a normal age-adjusted IGF-1 concentration not persistently achieved.

Basal LVMi was slightly increased in all patients, while earlier investigations give the LVMi as slightly reduced (27, 52). Our classification is based on the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging from 2015 (13). There normal LVMi is indicated <95 g/m² and 115 g/m², for female and male subjects, respectively. In contrast, the ULN used by Colao et al. (27, 52) was 110 g/m² and 135 g/m² for female and male patients, respectively. Thus, the differing references resulted in diverging classifications. The observed slightly abnormal LVMi in our patients was seen independently of pre-existing arterial hypertension. However, those with hypertension demonstrated higher LVMi than those without hypertension without the difference being significant (data not given).
The overall decline of the LVMi yielded interesting details after classification in two groups that is normal to mildly abnormal and moderately to severely abnormal (13). The percentage of male patients with moderately to severely abnormal LVMi increased and this would have been missed if only the mean or median LVMi were evaluated. This effect correlated with the IGF-1 delta during GH RT. that is a low initial IGF-1 concentration and a high IGF-1 concentration at year 2 resulted in an increased LVMi, indicating that the anabolic GH effect led to a relevant proportion of the patients with a moderately or severely increased left ventricular mass index. Thus, this long-term observation confirms concerns of a possible detrimental effect discussed, but not yet observed in the literature of short-term investigations (27, 30, 52).

The divergent results between male and female patients were evident for all echocardiographic parameters with more pronounced changes for male compared to female patients (data not given). This may indicate the relative resistance of female subjects to the effects of GH therapy. However, most female patients were postmenopausal without gonadal hormone substitution. No divergent results of GH RT on cardiac parameters for male vs female GHD patients have been reported so far (53, 54), possibly due to the mostly shorter observation periods. The clinical significance of these observations is unclear, as all patients had a normal EF, that is normal systolic function throughout.

Further analysis demonstrated that the decline of the NT-proBNP concentration during GH-R was mostly due to those patients with increased LVMi at the last follow-up. Whether the decline of NT-proBNP in this subgroup indicates subtle improvement of cardiac function not observed during echocardiographic evaluation remains an open question. The lower the IGF-1 concentration before therapy and the higher the achieved IGF-1 at year 3, the higher the risk of developing a moderately to severely increased LVMi. It is however noteworthy, that all patients had normal EF throughout GH-R. Would it be justified to suggest a lower therapeutic goal for patients with severe GHD to avoid overtreatment resulting in LVMi? It may well be that the cardiac hypertrophy observed during GH-R in these patients is a compensatory mechanism to overcome structural damage by GHD to uphold systolic function as indicated by the reduced NT-proBNP during GH-R.

### Conclusion

We performed a long-term observation on the effect of GH-R in patients with GHD on clinical status, NT-proBNP, a biomarker of heart failure and on LVM. None of the patients with GH-R developed signs of overt heart failure during follow-up. Patients with severe GHD had a continuous and significant decline of the NT-proBNP concentration during therapy, irrespective of a clinical diagnosis of cardiovascular disease. However, this was confined to patients with an increased LVMi at the last follow-up. NT-proBNP in these patients may reflect the structural myocardial changes due to GHD and the positive response to GH replacement (reversal of adverse remodelling). Whether the increase in cardiac hypertrophy reflects a necessary development in a structurally altered heart muscle or poses as a future risk factor for heart failure in GH-R will need further long-term study.

### Declaration of interest

U P participated in clinical registries on GH-R financed by Novo-Nordisk, Pfizer and Sandoz. The other authors have nothing to disclose.

### Funding

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### Author contribution statement

U P set up the investigation, cared for the patients, analysed the data and co-authored the manuscript, A Z compiled the data and co-authored the manuscript, D B analysed all echocardiographic data, W H discussed the cardiological data and co-authored the manuscript.

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**Table 4** Echocardiographic changes during GH replacement therapy: data from the literature.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Basal</th>
<th>During GH replacement therapy</th>
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<tbody>
<tr>
<td></td>
<td>Normal</td>
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</tr>
<tr>
<td>LVEDD</td>
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<td>(26)</td>
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<td>LVPWD</td>
<td>(28, 54, 55), this report</td>
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<td>EF</td>
<td>(30), this report</td>
<td>(6)</td>
</tr>
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</table>

*Compared to normal values.
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