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Benefit of Growth Hormone Replacement in Adults Older than 60 Years*

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ABSTRACT

Objective: Benefits of replacement therapy in growth hormone deficiency (GHD) are well documented in younger and middle-aged patients. The aim of our investigation was to prove the benefit of GH replacement for patients older than 60 years especially in terms of health-related quality of life (HRQoL) of age as well. **Design:** Data of 743 consecutively recruited patients (394 men, 349 women) with GHD aged 20 - 49 (n = 606) and 60 - 69 (n = 137) years enrolled from KIMS Germany (Pfizer International Metabolic Database) were compared. Treatment effects over the 12 months dose-finding and the subsequent phase up to three years were analysed using mixed models. Serum insulin-like growth factor I (IGF-I), fasting blood glucose, fasting serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) as well as body mass index (BMI) at baseline and at last visit were studied. HRQoL was assessed using the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA). **Results:** For both age groups and genders the IGF-I level and standardized IGF-I increased over the dose-finding phase. In women, the overall QoL-AGHDA score at the baseline examination was 8.7 (95% CI: 7.7 - 9.7) and decreased to 6.3 (95% CI: 5.1 - 7.6) at the end of the dose-finding phase ($p < 0.001$). In men, the corresponding values were 8.8 (95% CI: 7.8 - 9.8) and 6.4 (95% CI: 5.1 - 7.6; $p < 0.001$) without differences between the age groups. The therapy benefit for elderly was supported by the non-impairment after the dose-finding phase. In total cholesterol, LDL-C and fasting blood glucose, no significant changes were detected, whereas an increase in BMI did not differ between age groups. **Conclusion:** We could show positive effects of GH replacement on HRQoL in patients older than 60 years of age. Therefore, GH replacement should be considered in elderly GHD adults without difference compared to younger age groups.

Keywords: Growth Hormone Deficiency; Quality of Life; Growth Hormone; IGF-I

1. Introduction

Growth hormone deficiency (GHD) in adults is a well-recognized distinct clinical condition resulting from partial or complete pituitary failure and is characterized by increased fat mass [1], a decrease in lean body mass [2] and bone mineral density [3] as well as abnormal lipid metabolism [4,5]. Together, this metabolic changes result in an increased cardiovascular risk [6-9]. One of the most important impairment from a patient's point of view, however, is the decline in health-related quality of life (HRQoL) [10,11].

The availability of biosynthetic human growth hormone (GH) has made it possible to explore the effects and benefits of GH replacement therapy in adults with GHD. Some therapy effects, such as those on body competition or lipids, may be phase-specific. Recently, we demonstrated long-term beneficial effects of GH replacement therapy on HRQoL and showed no significant effects on total cholesterol, low-density lipoprotein cholesterol (LDL-C) or body mass index (BMI) [12]. For quality of life, only a few studies compared patients concerning short term GH responsiveness across older age-

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groups [13-16].

As the benefit for young and middle-aged patients is well-known, here we hypothesized a benefit for patients aged 60 years or older as well, possibly to a lower degree. Therefore, we analysed data from a German KIMS (Pfizer International Metabolic Database) population with a statistical method designed to handle intermittent missing observations.

2. Subjects and Method

2.1. Patient Characteristics

We analysed baseline and long-term data (range: 2 - 4 years) of 743 consecutively documented patients (394 men and 349 women) with GHD, aged 20 to 69 years, enrolled in KIMS Germany. The inclusion criterion for KIMS was the presence of GHD, confirmed by a relevant stimulation test. The therapy performance was monitored by the treating physicians. However, after an examination at baseline, the success of the therapy was individually adjusted in relation to IGF-I values, assuming one year for the dose-finding phase, in accordance with the guidelines [17,18]. An examination at the end of the dose-finding phase and a minimum of one visit per year were mandatory for each patient. Due to a change of IGF-I assays, 31st December 2005 was the qualifying date for the last examination. To analyse an observation period up to 4 years patients from March 1992 until 31st December 2001 were included. Sophisticated statistical models, namely mixed models, were used to deal with missing values. In women 1227.1 person-years and in men 1356.4 person-years of follow-up were observed. The mean time between the first and the last examination was 3.5 ± 0.8 years for female and 3.4 ± 0.9 years for male patients.

We analysed the causes of GHD at baseline in the 743 KIMS patients (**Table 1**). Childhood-onset (CO) GHD was reported in 192 patients (75 women and 117 men). Most patients (n = 551; 274 women and 277 men) had adult-onset (AO) GHD. The majority of patients had additional pituitary hormone replacement therapy at baseline. We detected adrenocorticotropic deficiency in 66.0% of patients aged 20 - 49 years and in 67.2% of patients aged 60 - 69 years. Therapy with thyroid hormones received 73.9% of patients aged 20 - 49 years and 69.3% of patients aged 60 - 69 years. Differentiation between thyrotrophic deficiency and thyroid disease was not possible. Therapy with sex hormones received 77.3% of male patients aged 20 - 49 years and 87.7% of male patients aged 60 - 69 years and 59.0% women aged 20 - 49 years and 41.1% of female patients aged 60 - 69 years. Therapy with sex hormones included any indication. Antidiuretic hormone was deficient in 30.4% of patients aged 20 - 49 years and in 13.9% of patients aged 60 - 69 years.

Table 1. Etiology of growth hormone deficiency in 743 patients.

	20 - 49 years (n = 606)		60 - 69 years (n = 137)	
	n	%	n	%
Idiopathic	74	12.2	5	3.6
Congenital	15	2.5	1	0.7
Non-functioning adenoma	131	21.6	87	63.5
Hormone secreting adenoma				
Prolactinoma	61	10.1	8	5.8
ACTH-om/Cushings diseases	35	5.8	5	3.6
GH-om	8	1.3	1	0.7
TSH-om	0	0.0	1	0.7
Gonadotropin-secreting	2	0.3	0	0.0
Craniopharyngioma	107	17.7	8	5.8
Tumor nearby pituitary/hypothalamus	25	4.1	3	2.2
Pituitary abscess	2	0.3	0	0.0
Rathke cyst	12	2.0	1	0.7
Hypophysitis	8	1.3	2	1.5
Traumatic brain injury	35	5.8	1	0.7
Sheehan syndrome	19	3.1	4	2.9
Empty sella syndrome	14	2.3	6	4.4
Cranial tumor distant from pituitary/hypothalamus	16	2.6	2	1.5
CNS infection	8	1.3	0	0.0
Granulomatous diseases	3	0.5	0	0.0
Vascular diseases	3	0.5	1	0.7
Others	28	4.6	1	0.7

Patients were examined for IGF-I, fasting blood glucose, total cholesterol, LDL-C, BMI and HRQoL at baseline (**Tables 2** and **3**) and at the last follow-up visit. BMI was calculated based on height and body weight. HRQoL was determined using the adult GH deficiency assessment (QoL-AGHDA) score. This is a cross-cultural, disease-specific, one-dimensional, patient needs-based questionnaire specifically developed for GHD patients [19]. QoL-AGHDA focuses on those aspects of HRQoL that seem most relevant to adult GHD patients and detects deficits in areas that are affected in adults with GHD.

2.2. Laboratory Methods

Blood samples were drawn to measure IGF-I, glucose, total cholesterol and HDL-C. LDL-C were estimated using Friedewald's formula [20]. Serum lipoproteins and IGF-I were measured centrally in the KIMS laboratory as described previously [21-23]. Until November 2002, serum IGF-I was determined by radioimmunoassay after acid-ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Thereafter, a chemiluminescence immunoassay (Nichols Advantage System, San Clemente, CA, USA) was introduced. IGF-I values were adjusted for age and gender and expressed as standardized deviation score (SDS). Blood glucose was analysed locally by routine laboratory techniques.

2.3. Statistical Analysis

In preliminary analyses, patients were classified into age groups of ten years. The available data from age group of 50 - 59 years were too small (n = 3) to estimate effects of desirable precision and therefore excluded for further analysis. To facilitate the readability we decided to present two age groups: younger than 50 years and older than 60 years. According to the study guideline the period of GH replacement therapy of four years was divided into a dose-finding phase over the first 12 months and the following preservation phase over three years.

Analyses were performed with STATA/MP software, version 10.1 (StataCorp LP, College Station, Texas, USA). Baseline characteristics are expressed as mean and standard deviation (SDS). Solely to show a proxy for the estimated change, we present time points for descriptive statistics and figures. Time was rounded up to the nearest year, except for the baseline examination and within the first year (which was rounded up to the half-year). The 95% confidence intervals (CI) were adjusted for clusters in patients using the "mean" procedure.

To estimate changes in IGF-I levels or other outcomes we took the exact time (years with appropriate number of digits) by using linear mixed models instead of rounded time points, as done in conventional models. Mixed models use all available data, properly account for correlation between repeated measurements and properly deal with missing data if the missing at random (MAR) assumption is met. In longitudinal studies, however, it is often reasonable to assume that the intermittent missing observations are randomly missing [24]. For missing baseline values, corresponding tests were performed in preliminary analyses. As the number of missing values at each examination differed across outcomes, the available numbers of patients and observations were presented outcome-specifically at the place of the given analysis.

For the dose-finding phase and the preservation phase, we modeled slopes for the change in levels of each dependent variable, resulting in a so-called discontinuous slope model, described by Singer *et al*. [25]. To model the baseline value, we included the intercept and age at baseline as fixed effects. To quantify the change over the two phases adequately, we included continuous time and continuous time after 1 year as fixed effects. Continuous time, continuous time after 1 year and the intercept were included as variance components or random effects. To obtain the change over the second phase the corresponding linear combination was computed. For the linear mixed models we used the GLLAMM [26] procedure. The assumptions of the models were examined analytically and graphically and were adequately met, except for QoL-AGHDA score as an outcome. Therefore, results of negative binomial regression models were presented for QoL-AGHDA. An improvement in QoL-AGHDA is indicated by negative coefficients. For the negative binomial regression the "xtnbreg" procedure was used.

3. Results

3.1. GH Dose

The dose of GH increased over the dose-finding phase and was nearly constant over the preservation phase. The mean dose of GH at the beginning of preservation phase was 0.42 ± 0.01 mg per day for females (n = 531) and 0.40 ± 0.02 mg per day for males (n = 563) for patients aged 20 - 49 years. For the elderly the mean dose of GH at the beginning at the preservation phase was 0.25 ± 0.03 mg per day in females (n = 105) and 0.30 ± 0.02 mg per day in males (n = 149).

3.2. Serum IGF-I

The detailed results are presented in **Table 4** and **Figures 1(c)** and **(d)**. The baseline IGF-I values (**Tables 2** and **3**) did not differ across age groups (females: $p = 0.557$; males: $p = 0.699$) whereas standardized IGF-I values differed (both genders: $p < 0.01$). For both age groups and genders, the IGF-I absolute concentrations and IGF-I SDS increased over the dose-finding phase. In females

Table 2. Observed values for different parameters of female KIMS patients over an observation period of 4 years.

	Females aged 20 - 49 years						Females aged 60 - 69 years					
	Dose-finding phase			Preservation phase			Dose-finding phase			Preservation phase		
Time [years]	0	1/2	1	2	3	4	0	1/2	1	2	3	4
Age [years]*	36.6 ± 8.4 n = 293						63.4 ± 2.5 n = 56					
Dose [mg/day]	0.26 ± 0.02 n = 250	0.32 ± 0.01 n = 550	0.43 ± 0.02 n = 333	0.43 ± 0.01 n = 531	0.43 ± 0.02 n = 409	0.44 ± 0.02 n = 362	0.18 ± 0.03 n = 46	0.28 ± 0.02 n = 120	0.30 ± 0.03 n = 55	0.25 ± 0.03 n = 105	0.31 ± 0.04 n = 80	0.30 ± 0.04 n = 60
Quality of Life AGHDA score	8.6 ± 0.6 n = 137	9.8 ± 1.0 n = 45	6.2 ± 0.7 n = 79	5.6 ± 0.5 n = 158	6.4 ± 0.5 n = 149	5.9 ± 0.6 n = 137	9.1 ± 1.3 n = 29	7.2 ± 2.2 n = 10	6.9 ± 1.5 n = 17	5.7 ± 0.9 n = 41	4.5 ± 1.2 n = 25	5.6 ± 1.3 n = 27
IGF-I [ng/ml]	108.9 ± 8.1 n = 106	161.5 ± 9.1 n = 168	184.4 ± 8.7 n = 129	179.3 ± 8.3 n = 181	178.5 ± 7.3 n = 180	173.5 ± 8.4 n = 180	98.9 ± 11.9 n = 28	140.2 ± 12.3 n = 44	144.1 ± 19.0 n = 16	152.2 ± 11.7 n = 44	136.7 ± 9.7 n = 43	138.3 ± 16.4 n = 31
IGF-I-SDS	−2.4 ± 0.2 n = 106	−0.9 ± 0.2 n = 168	−0.5 ± 0.2 n = 129	−0.5 ± 0.2 n = 181	−0.3 ± 0.1 n = 180	−0.3 ± 0.1 n = 180	−0.9 ± 0.3 n = 28	0.1 ± 0.2 n = 44	0.1 ± 0.4 n = 16	0.4 ± 0.2 n = 44	0.2 ± 0.2 n = 43	0.3 ± 0.3 n = 31
Total cholesterol [mmol/l]	5.7 ± 0.1 n = 100	5.7 ± 0.2 n = 113	5.7 ± 0.1 n = 97	5.7 ± 0.1 n = 162	5.7 ± 0.1 n = 173	5.6 ± 0.1 n = 175	6.2 ± 0.2 n = 28	6.2 ± 0.2 n = 33	5.7 ± 0.3 n = 15	6.0 ± 0.2 n = 42	6.0 ± 0.2 n = 36	5.7 ± 0.2 n = 29
LDL cholesterol [mmol/l]	3.4 ± 0.1 n = 94	3.4 ± 0.1 n = 104	3.3 ± 0.1 n = 91	3.3 ± 0.1 n = 156	3.3 ± 0.1 n = 165	3.3 ± 0.1 n = 168	3.9 ± 0.2 n = 25	3.8 ± 0.2 n = 30	3.4 ± 0.2 n = 15	3.6 ± 0.1 n = 41	3.6 ± 0.1 n = 35	3.3 ± 0.2 n = 29
Blood glucose [mg/dl]†	80.6 ± 1.6 n = 36	82.1 ± 3.5 n = 29	85.3 ± 1.6 n = 31	84.8 ± 2.3 n = 63	84.6 ± 2.5 n = 46	85.1 ± 2.2 n = 48	100.5 ± 5.9 n = 8	87.0 ± 5.5 n = 7	85.3 ± 6.3 n = 3	88.9 ± 5.1 n = 9	94.5 ± 13.0 n = 8	99.0 ± 12.3 n = 4
Body mass index [kg/m²]	27.5 ± 0.4 n = 276	28.5 ± 0.6 n = 367	28.3 ± 0.5 n = 275	28.1 ± 0.5 n = 466	28.3 ± 0.6 n = 390	29.3 ± 0.6 n = 315	29.1 ± 0.6 n = 52	29.1 ± 0.7 n = 69	28.0 ± 0.7 n = 42	28.8 ± 0.7 n = 88	29.4 ± 0.8 n = 74	29.2 ± 0.9 n = 57

AGHDA: Assessment of GHD in Adults; IGF-I: insulin-like growth factor I; SDS: standard deviation score; LDL: low-density lipoprotein; mean ± standard error adjusted for multiple observations in patients are given, numbers are related to the numbers of observations; *for age, mean ± standard deviation are given; †fasting, plasma glucose.

Table 3. Observed values for different parameters of male KIMS patients over an observation period of 4 years.

	Males aged 20 - 49 years						Males aged 60 - 69 years					
	Dose-finding phase			Preservation phase			Dose-finding phase			Preservation phase		
Time [years]	0	1/2	1	2	3	4	0	1/2	1	2	3	4
Age [years]*	35.5 ± 8.5 n = 313						64.2 ± 3.1 n = 81					
Dose [mg/day]	0.29 ± 0.02 n = 264	0.32 ± 0.01 n = 561	0.39 ± 0.02 n = 324	0.40 ± 0.02 n = 563	0.38 ± 0.02 n = 449	0.40 ± 0.02 n = 361	0.22 ± 0.02 n = 67	0.29 ± 0.02 n = 143	0.30 ± 0.03 n = 81	0.30 ± 0.02 n = 142	0.30 ± 0.03 n = 122	0.29 ± 0.04 n = 89
Quality of Life AGHDA score	8.9 ± 0.6 n = 154	6.5 ± 0.8 n = 54	6.6 ± 0.7 n = 84	6.1 ± 0.5 n = 202	5.6 ± 0.5 n = 156	4.6 ± 0.5 n = 143	8.3 ± 1.2 n = 31	6.4 ± 1.3 n = 11	5.4 ± 1.5 n = 20	6.1 ± 0.9 n = 51	5.9 ± 0.9 n = 43	4.4 ± 0.7 n = 29
IGF-I [ng/ml]	131.6 ± 9.6 n = 119	189.1 ± 8.6 n = 210	219.4 ± 11.4 n = 139	232.7 ± 9.5 n = 225	241.5 ± 10.8 n = 211	240.9 ± 10.5 n = 170	124.0 ± 12.9 n = 32	191.1 ± 13.4 n = 56	240.7 ± 19.4 n = 29	199.2 ± 13.4 n = 59	188.7 ± 12.0 n = 53	192.1 ± 12.9 n = 42
IGF-I-SDS	−2.0 ± 0.2 n = 119	−0.8 ± 0.2 n = 210	−0.1 ± 0.2 n = 139	0.1 ± 0.1 n = 225	0.3 ± 0.2 n = 211	0.4 ± 0.1 n = 170	−0.4 ± 0.3 n = 32	0.9 ± 0.2 n = 56	1.6 ± 0.2 n = 29	1.1 ± 0.2 n = 59	0.9 ± 0.2 n = 53	1.0 ± 0.2 n = 42
Total cholesterol [mmol/l]	5.7 ± 0.1 n = 111	5.4 ± 0.2 n = 112	5.5 ± 0.1 n = 96	5.5 ± 0.1 n = 194	5.5 ± 0.1 n = 195	5.5 ± 0.1 n = 155	5.7 ± 0.1 n = 29	5.3 ± 0.2 n = 37	5.5 ± 0.2 n = 23	5.2 ± 0.2 n = 52	5.4 ± 0.1 n = 48	5.6 ± 0.2 n = 37
LDL cholesterol [mmol/l]	3.5 ± 0.1 n = 99	3.4 ± 0.2 n = 104	3.4 ± 0.1 n = 87	3.4 ± 0.1 n = 180	3.4 ± 0.1 n = 186	3.3 ± 0.1 n = 146	3.8 ± 0.1 n = 28	3.2 ± 0.2 n = 37	3.4 ± 0.2 n = 23	3.2 ± 0.2 n = 52	3.3 ± 0.1 n = 47	3.5 ± 0.2 n = 37
Blood glucose [mg/dl]†	80.9 ± 2.2 n = 38	83.1 ± 2.4 n = 43	83.0 ± 1.7 n = 37	85.8 ± 2.1 n = 69	81.0 ± 1.6 n = 50	82.5 ± 1.5 n = 40	88.7 ± 2.0 n = 12	95.6 ± 2.1 n = 7	93.4 ± 7.0 n = 14	98.6 ± 7.7 n = 24	92.9 ± 2.8 n = 27	94.6 ± 13.7 n = 11
Body mass index [kg/m²]	27.4 ± 0.3 n = 294	27.5 ± 0.5 n = 374	27.0 ± 0.4 n = 264	27.9 ± 0.4 n = 496	27.8 ± 0.4 n = 397	28.0 ± 0.4 n = 326	28.5 ± 0.4 n = 75	28.6 ± 0.8 n = 102	28.0 ± 0.6 n = 63	28.7 ± 0.6 n = 123	28.5 ± 0.5 n = 109	28.6 ± 0.5 n = 73

AGHDA: Assessment of GHD in Adults; IGF-I: insulin-like growth factor I; SDS: standard deviation score; LDL: low-density lipoprotein; mean ± standard error adjusted for multiple observations in patients are given, numbers are related to the numbers of observations; *for age, mean ± standard deviation are given; †fasting, plasma glucose.

Table 4. IGF-I and standardized IGF-I across time for females and males: coefficients or linear combinations and standard errors of changes (linear mixed models).

	Age group	
	20 - 49 years	60 - 69 years
IGF-I		
Females (*n* = 272; 1150 *observations*)	(n = 227; 944 obs.)	(n = 45; 206 obs.)
Dose-finding phase		
Change	66.8 (8.0)‡	36.5 (16.6)*
Difference in change compared with group aged 20 - 49 years	---	−30.3 (18.5)
Preservation phase		
Change	−10.8 (3.7)†	−7.6 (8.5)
Difference in change compared with group aged 20 - 49 years	---	3.1 (9.3)
Males (*n* = 303; 1345 *observations*)	(n = 239; 1074 obs.)	(n = 64; 271 obs.)
Dose-finding phase		
Change	74.8 (8.4)‡	61.6 (16.5)‡
Difference in change compared with group aged 20 - 49 years	---	−13.2 (18.6)
Preservation phase		
Change	−4.0 (3.9)	−9.5 (8.2)
Difference in change compared with group aged 20 - 49 years	---	−5.5 (9.1)
IGF-I standardized		
Females (*n* = 272; 1150 *observations*)		
Dose-finding phase		
Change	1.6 (0.2)‡	0.9 (0.3)†
Difference in change compared with group aged 20 - 49 years	---	−0.7 (0.4)*
Preservation phase		
Change	−0.1 (0.1)	0.0 (0.1)
Difference in change compared with group aged 20 - 49 years	---	0.1 (0.2)
Males (*n* = 303; 1345 *observations*)		
Dose-finding phase		
Change	1.5 (0.2)‡	1.1 (0.3)‡
Difference in change compared with group aged 20 - 49 years	---	−0.4 (0.3)
Preservation phase		
Change	0.0 (0.1)	−0.1 (0.1)
Difference in change compared with group aged 20 - 49 years	---	−0.1 (0.1)

*$p < 0.05$; †$p < 0.010$; ‡$p < 0.001$.

the change during the dose-finding phase was greater in the group aged 20 - 49 years compared with the older age group. In males no age-related change occurred. The possibly relevant difference in change of IGF-I levels between males and females did not reach statistical significance, neither for elderly nor for non-elderly. Over the preservation phase, changes in standardized IGF-I were not statistically significant.

3.3. HRQoL

In each age group of both genders the QoL-AGHDA score decreased over the dose-finding phase and remained stable over the preservation phase except for females younger than 50 years of age (**Table 5**, **Figures 1(a)** and **(b)**). In males and females the rates of QoL-AGHDA score over the dose-finding phase were almost the same in both age groups. Females showed a higher rate of reduction of QoL-AGHDA-scores than males ($p = 0.045$; 647 subjects). In women the overall observed mean QoL-AGHDA score at the baseline examination was 8.7 (95% CI: 7.7 - 9.7) and decreased to 6.3 (95% CI: 5.1 - 7.6) at the end of the dose-finding phase ($p < 0.001$). In men the overall mean QoL-AGHDA score decreased from 8.8 (95% CI: 7.8 - 9.8) at the baseline examination to 6.4 (95% CI: 5.1 - 7.6) at the end of the dose-finding phase ($p < 0.001$). In ancillary analyses we included the onset of GHD (CO and AO) in the model. Differences in change between the two onset groups did not occur. But over the total period of four years the QoL-AGHDA score was lower in subjects with CO than in those with AO (difference in females: 0.57, 95% CI: 0.21 - 0.93; $p = 0.002$; difference in males: 0.32, 95% CI: 0.02 - 0.62; $p = 0.034$).

3.4. Blood Glucose, Lipid Profile and Anthropometry

For total cholesterol and LDL-C, glucose and BMI a discontinuous slope model is not needed but a linear model with one single slope over both phases can be assumed. To examine phase-specific relationships we analyzed discontinuous slope models as well. For blood glucose and lipids we did not find statistically significant changes.

Changes in BMI did not differ across age groups. The overall estimates yielded no relevant changes over dose-finding phase (females: 0.04 kg/m^2, 95% CI: −0.22 - 0.29, $p = 0.769$, $n = 349$ with 2471 observations; males: 0.08 kg/m^2, 95% CI: −0.12 - 0.27, $p = 0.426$, $n = 394$ with 2696 observations). Over the preservation phase females and males similarly increased in BMI (females: 0.30 kg/m^2 per year, 95% CI: 0.17 - 0.44, $p < 0.001$; males: 0.29 kg/m^2 per year, 95% CI: 0.18 - 0.39, $p < 0.001$).

4. Discussion

Positive effects of GH replacement therapy in GHD patients are widely accepted [17]. Here, we demonstrate positive therapy effects on HRQoL in a large cohort of

Table 5. AGHDA score across time for females and males: coefficients or linear combinations and standard errors of changes (Negative binomial regression).

	Age group	
	20 - 49 years	60 - 69 years
Females (*n* = 298; 854 *observations*)	(n = 248; 705 obs.)	(n = 50; 149 obs.)
Dose-finding phase		
Change	−0.54 (0.06)‡	−0.53 (0.13)‡
Difference in change compared with group aged 20 - 49 years	---	−0.01 (0.14)
Preservation phase		
Change	0.06 (0.03)*	−0.06 (0.07)
Difference in change compared with group aged 20 - 49 years	---	−0.12 (0.08)
Males (*n* = 349; 978 *observations*)	(n = 277; 793 obs.)	(n = 72; 185 obs.)
Dose-finding phase		
Change	−0.34 (0.05)‡	−0.37 (0.11)†
Difference in change compared with group aged 20 - 49 years	---	−0.03 (0.12)
Preservation phase		
Change	−0.02 (0.03)	−0.02 (0.06)
Difference in change compared with group aged 20 - 49 years	---	0.00 (0.06)

*$p < 0.05$; †$p < 0.010$; ‡$p < 0.001$.

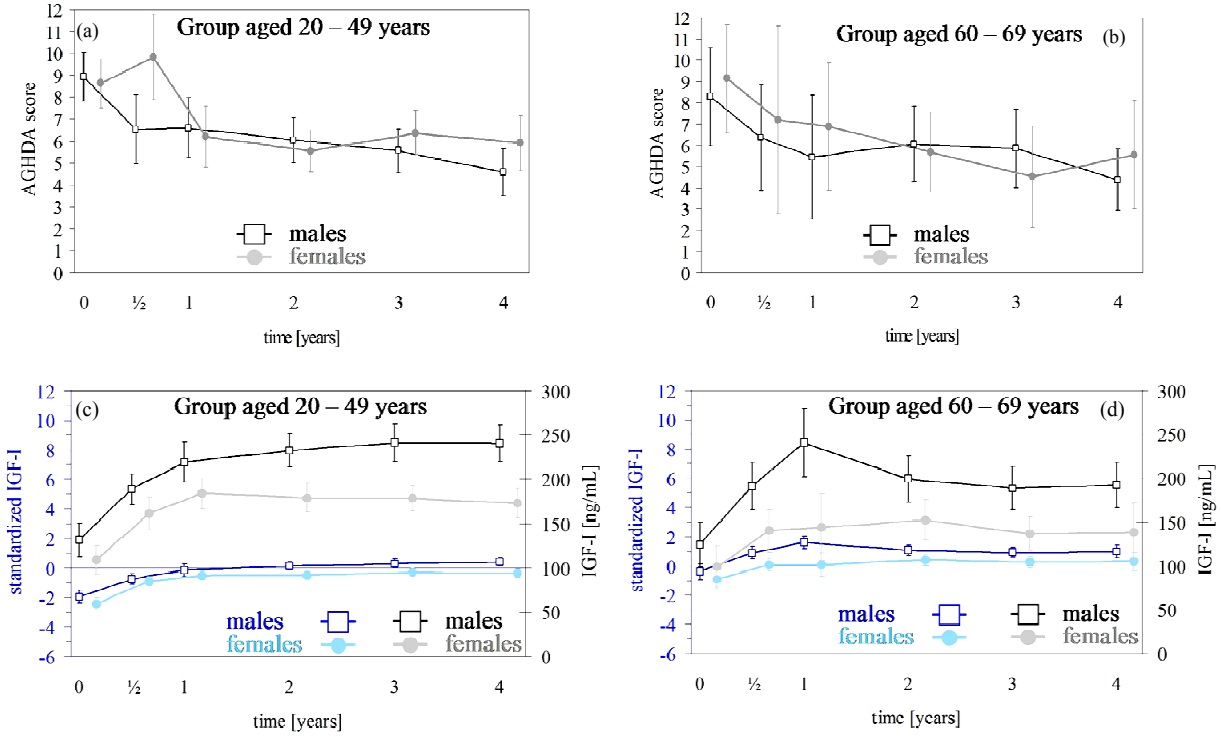

Figure 1. (a), (b) AGHDA scores (male: black; female: grey) with 95% confidence intervals (CI) over a maximum of four years for a total of 298 females with 854 observations and 349 males with 978 observations. Time except for the baseline examination was rounded up to whole year but within the first year up to half-year. The 95% CI are adjusted for correlated observations within patients. (c) and (d) IGF-I levels (male: black; female: grey) and standardized IGF-I levels (male: blue; female: light blue) with 95% confidence intervals (CI) over a maximum of four years for a total of 272 females with 1150 observations and 303 male completers with 1345 observations. Time except for the baseline examination was rounded up to whole year but within the first year up to half-year. The 95% CI are adjusted for correlated observations within patients.

patients older than 60 years of age as well. Our results are confirmed by a recent metaanalysis of 11 eligible studies with a total of 534 patients [27]. However, only 2 of these 11 studies prospective, based on a randomized, placebo-controlled study design with a duration of 6 (N = 15) or 12 months (N = 62), respectively.

In our study both age groups, middle aged as well as older patients and genders had decreased QoL-AGHDA-scores after one year of GH therapy than at baseline and this improvement remained up to four years. Interestingly, the improvement in HRQoL was restricted to the dose-finding phase [13,28,29]. The level of improvement was substantially the same across elderly and non-elderly [13,15,16], but in contrast to our study, mostly cohorts of elderly were analysed in the metaanalysis only up to 12 months (8 studies N = 422 patients).

The benefit of the therapy for elderly is additionally supported by the non-impairment after the dose-finding phase and went confirm with other long-term studies of mixed age-groups up to nine years with smaller cohorts [29-35]. Gibney *et al*. [36] showed an improvement over a period of 10 years but only for a very small cohort (n = 11). Females improved more than males [28], in contrast to other findings [29], without any gender-differences. Kendall-Taylor *et al*. [37] found a greater impairment HRQoL in AO patients than in CO patients at baseline. Rosilio *et al*. [14] detected this difference after one year of GH-replacement, but not during the following year, that could be due to a very small number of CO patients [38,39]. However, after four years of GH replacement, we found a greater improvement in CO patients in comparison to the AO cohort [40] in contrast to Bengtsson *et al*. [28]. They detected an improvement in HRQoL only in AO patients.

Previous long-term studies of GH replacement compared HRQoL values of different countries. Koltowska-Häggstrom and colleagues analysed 758 patients up to seven years [31]. HRQoL already improved during the first year and remained constant in the follow up. They compared their results with large cohorts from England/Wales, the Netherlands, Spain and Sweden with a minimum duration of two years up to a maximum of seven years. HRQoL was impaired in comparison with healthy controls and improved in all countries. Saller *et al*. found no differences between the improvements in HRQoL of the Netherlands, Sweden and Germany [35].

Moock *et al*. [41] demonstrated no correlation between IGF-I serum concentration and AGHDA scores for a German cohort. The increase and normalization of IGF-Ilevels in the present analysis are consistent with many other studies [33,36,40,42-50]. A gender-related benefit was detected by others [29,51,52] and for long-term stud- ies as well [53-55]. This gender difference regarding IGF-I levels was present in our data but without confi- dence. The most likely reason might be the postmeno- pausal status in our patient goup. The rate of change re- garding standardized IGF-I values, however, was sub- stantially the same in males and females over both phases. In addition, the rate of change over the preservation phase was the same as for healthy males or females. Re- markably, although female and male patients aged 60 to 69 years were in or close to normal ranges at baseline we found a positive therapy effect on QoL in this age group. As mentioned in the result in elderly the GH dosage was significant lower than in the younger age groups.

In elderly, however, normal IGF-I levels are no excluding criteria of GHD presence [17]. Hilding *et al*. [56] observed normal IGF-I values at baseline with increasing age. The percentage of normal IGF-I baseline values increased from 4% of 20 - 39 years old patients up to 40% in the group over 60 years. It is well known that in the elderly GH secretion decreases, associated with a decline in IGF1 levels. Therefore, age-adjusted IGF-I SD-scores are necessary to be able to assess the treatment response to rhGH as in our study using IGF-I SD-scores established in a central laboratory with adequate reference ranges established in healthy controls even in the elderly.

This study also assessed the lipid profile and no change was found and went confirm with others [42,53,57]. Other studies detected a decrease for total cholesterol in all age-groups and both genders [15,46,54]. Generally, LDL-C showed a trend to decrease as described in some long-term studies of GH replacement therapy [36,58] also in patients over 65 years of age [59]. High baseline values or high dose of GH replacement could be reasonable for that. In the recent metaanalysis [27] treatment with rhGH in elderly showed a lowering effect on total and LDL cholesterol. Again, most of the patients (N = 422 out of 534 patients) were observed for 12 months or less. Moreover, blood glucose levels were independent of age, which is in line with four previous studies [36,42,53,57].

During GH therapy the BMI increased over the preservation phase without difference between elderly and non-elderly. Changes over dose-finding phase were very small and showed no gender-related differences [53,54,60]. However, constant BMI levels were measured by Giusti *et al*. [47]. In summary, our results in the elderly confirm the data of Spielhagen *et al*. [12] that demonstrated also no significant effects on total cholesterol, LDL-C or anthropometric parameters like BMI in a long term observation. From this point of view, it is uncertain whether the previous reported beneficial effects of GH treatment lipids and body composition can be translated into decreased cardiovascular events or morbidity and mortality. However, another group demonstrated recently that two years of GH replacement decreased cardiovascular risk estimates approximately by half [61]. In this study male sex, high total and low HDL cholesterol levels are potential predictors of good response, whereas, in large epidemiological studies the addition of biomarker information did not affect the association of subjective health measures, like SF12 or QoL-AGHDA, with mortality, but significantly improved risk stratification. Thus, a combined assessment of self-reported subjective health and measured biomarkers may be useful to identify high-risk individuals for intensified monitoring [62].

One limitation of our study is the lack of a control group. For IGF-I, however, the zero level of standardized IGF-I may serve as an adequate comparison. Moreover, a quasi-control group within subjects was generated by separating the study period into dose-finding and presservation phase. If the change during the dose-finding phase is different from those over the preservation-phase, the specificity of the treatment effect will be supported. This was clearly met for IGF-I and AGHDA scores. A second limitation is the absence of the group aged 50 - 59 years. For this age group only assumptions can be made.

In conclusion, we have shown that HRQoL was improved not only in younger GHD patients but elderly perceived benefits as well, which have been confirmed by small sized randomized controlled trials as well as by a recent metaanalysis. Therefore, GH therapy should not only be offered to young and middle-aged GHD patients. There seems to be no age limitation in treating elderly GHD adults with GH, especially in view of QoL measures. Not only a long life but also to facilitate for growing old in dignity should be the ambition of medical therapy. Whereas, the question, if the effect of long term GH treatment in the elderly on cardiometabolic outcomes is clinically relevant, remains under discussion and might be better solved in further randomized controlled trials.

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