

ORIGINAL ARTICLE

Sleep apnoea and quality of life in growth hormone (GH)-deficient adults before and after 6 months of GH replacement therapy

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Summary

Objective To investigate the sleep architecture and breathing as well as quality of life (QoL) in adults with GH deficiency (GHD) before and 6 months after GH replacement therapy.

Design A prospective observational study.

Patients Nineteen consecutive adults with GHD (11 men, eight women; mean age 53, range 21–73 years) were studied.

Measurements An overnight sleep study was performed and the Minor Symptom Evaluation Profile (MSEP), Functional Outcome of Sleep Questionnaire (FOSQ), Short Form 36 (SF-36) and Epworth Sleepiness Scale (ESS) questionnaires were applied at baseline and after the treatment period.

Results For the whole group, there were no significant changes in mean total sleep time (TST; 370 min vs. 374 min), proportion of slow-wave sleep (SWS; 17.8% vs. 18.4%) and rapid eye movement (REM) sleep (12.1% vs. 13.9%) on GH replacement. Mean apnoea–hypopnoea index (AHI) was high and remained unchanged (28.2/h before vs. 28.0/h following GH replacement). Twelve patients (63%) were found to have obstructive sleep apnoea (OSA; AHI \geq 10/h) at baseline. Compared with GH-deficient patients without OSA (AHI 3.9/h), the OSA patients (AHI 42.4/h) had less SWS (11.4% vs. 28.6%, $P = 0.010$) and REM sleep (10.1% vs. 15.5%, $P = 0.036$). A marginal increase was observed in REM sleep time (10.1% before vs. 12.7% after GH; $P = 0.048$) while SWS was unchanged in this group. Moreover, MSEP for General Well-being and Responsiveness, FOSQ scores for General Productivity, Activity Level and Vigilance as well as SF-36 domains for Vitality and Mental Health were improved.

Conclusions Contrary to some previous observations in a smaller group of patients, our data suggest that GH therapy does not induce or aggravate OSA in GH-deficient adults. Moreover, GH therapy may improve some of the QoL dimensions in these patients.

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Introduction

The secretion of GH is pulsatile and episodic with a low average of GH secretion in the daytime and higher GH secretion during sleep.¹ There is extensive evidence for a consistent relationship between slow-wave sleep (SWS) and increased pulsatile GH secretion, and conversely, between awakening and decreased GH release.^{2,3} In sleep disordered breathing (SDB), especially in obstructive sleep apnoea (OSA), the sleep architecture is disturbed, resulting in impaired SWS, frequent arousals and sleep stage changes. Pulsatile GH secretion has been observed to be low in OSA patients, and the treatment of OSA with continuous positive airway pressure (CPAP) may improve the sleep architecture, increase SWS and GH secretion.⁴ In children, surgical correction of OSA may restore GH secretion and normal growth rate.⁵

There is also some evidence of the involvement of the somatotrophic axis in the regulation of sleep quality. In an early study in normal human subjects, an intramuscular GH injection administered 15 min before bedtime was shown to stimulate rapid eye movement (REM) sleep.⁶ In another study with eight patients with isolated GH deficiency (GHD), GH replacement therapy decreased total sleep time (TST) and increased the REM sleep.⁷ However, in a more recent study of 18 adults with GHD, no significant change in sleep architecture was detected following 6 months of GH therapy.⁸

Little is known of the prevalence of OSA in GH-deficient adults. However, in adults with active acromegaly, OSA is common and improved with cure or biochemical control of the GH excess.^{9,10} The concern has therefore been that GH replacement therapy might induce or deteriorate OSA. A recent case report suggested onset of severe OSA in an adult male patient during GH replacement therapy, and a consequent study of five middle-aged men with GHD revealed a decrease in SWS and a shift from obstructive to central apnoea and hypopnoea upon cessation of GH replacement.¹¹ This suggests that GH may impact on sleep in a complex action by affecting both sleep and breathing through the central nervous system and the upper airways.

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Patients with GHD have compromised quality of life (QoL),¹² which improves with GH replacement therapy.¹³ However, individual responsiveness to GH replacement is varied and to some extent explained by age, gender and body mass index (BMI) in terms of changes in IGF-I and body composition.¹⁴ As high BMI at baseline was found to be a predictor of poor response to GH treatment,¹⁴ and as obesity is a common finding in OSA,¹⁵ it may be speculated that concomitant OSA in obese GH-deficient patients, rather than obesity *per se*, might be responsible for the poor response to GH replacement in terms of QoL and well-being in some patients.

In the current prospective study, the aim was to analyse polysomnographic (PSG) findings and QoL in a consecutive clinical cohort of GH-deficient adults before and after 6 months of GH replacement therapy. We also addressed the question of whether OSA could explain poor responsiveness to GH replacement therapy in terms of QoL and well-being.

Methods

Study population

Nineteen consecutive adults (11 men and eight women; mean age 53; range 21–73 years) were studied. All had acquired hypopituitarism and GHD in adulthood that was verified with a peak GH response < 3 µg/l during an insulin tolerance test. The patients were recruited from the outpatient ward at the Research Centre for Endocrinology and Metabolism at the Sahlgrenska University Hospital, Gothenburg, Sweden. The cause of GHD was nonfunctioning pituitary adenoma (NFPA) in 12 patients, secreting pituitary adenoma in three (Cushing's syndrome in two and prolactinoma in one), craniopharyngioma in two, Rathke's cyst in one and hypophysitis in one patient. Fourteen patients had received transsphenoidal pituitary surgery and four had been treated with transfrontal surgery. Three patients had received radiotherapy. Five patients had one additional anterior pituitary hormonal deficiency, seven patients had two additional deficiencies, and eight patients had three additional deficiencies. Four patients had diabetes insipidus. All patients received, when necessary, replacement therapy with corticosteroids, thyroxine and desmopressin. All gonadotrophin-deficient men received testosterone replacement. Five (62%) of the eight women with hypogonadism received oestrogen treatment. The hormonal replacement therapies were kept constant during the study period.

Ethical considerations

The local ethics committee approved the study and all patients gave written informed consent before entering the study.

Protocol

Patients were studied before and after 6 months of GH replacement therapy. GH was administered as a daily bedtime subcutaneous injection. The GH dose was individualized with the aim of normalizing serum IGF-I concentration and body composition.¹⁶ Patients were hospitalized at baseline and after 6 months for anthropometric measurements, questionnaires and PSG investigations (see below),

and fasting concentrations of IGF-I, glucose, insulin, lipids and haemoglobin A_{1c} (HbA_{1c}). Body weight was measured in the morning to the nearest 0.1 kg, and body height was measured barefoot to the nearest 0.01 m. BMI was calculated as the weight in kilograms divided by the height in metres squared. Waist circumference was measured in the standing position with a flexible plastic tape placed midway between the lower rib margin and the iliac crest, and hip girth was measured at the widest part of the hip.

Overnight sleep studies

Before the start and after 6 months of GH replacement, a full-night PSG recording was performed using a computerized recording system (Embla A10©, Flaga, Reykjavik, Iceland) consisting of: (1) sleep monitoring through three-channel electroencephalography (EEG; C4/A1, C3/A2, CZ/A1), two-channel electrooculography (EOG) and one-channel submental electromyography (EMG); (2) bilateral tibial EMG and a body-position detector; (3) a two-lead electrocardiogram; and (4) respiration monitoring through a thermistor as well as a nasal pressure sensor for apnoea–hypopnoea detection, piezo-crystal effort belts for thoraco-abdominal movement detection and a pulse-oximeter (Embla Oximeter-XN). Sensors were placed and equipment was calibrated at the Sleep Laboratory of the Sahlgrenska University Hospital by a certified sleep technician and all recordings took place at the Research Centre for Endocrinology and Metabolism. Following equipment retrieval the next morning, the data, stored in real time on PCMCIA cards, were downloaded to the computers at the sleep laboratory and subsequently scored based on 30-s epochs according to the criteria of Rechtschaffen and Kales.¹⁷ An overall sleep stage report and accurate measures of respiratory events during the sleeping period were generated. An obstructive apnoea was defined as a flat nasal pressure signal accompanied by respiratory effort movement for ≥ 10 s. An obstructive hypopnoea was defined as a ≥ 50% reduction in the nasal pressure signal accompanied by respiratory effort movement for ≥ 10 s. The number of apnoeas and hypopnoeas per hour of sleep (the apnoea–hypopnoea index, AHI) was calculated and OSA was defined as an AHI of at least 10/h. Additionally, the total number of significant oxygen desaturations (drop in oxygen saturation by at least 4% from the immediately preceding baseline) was scored. The oxygen desaturation index (ODI) was calculated as the number of significant desaturations per hour of sleep, and the lowest oxygen saturation (Sat. min) during the overnight recording was determined. The data were scored blinded to the status of the patients.

Questionnaires

The Minor Symptom Evaluation Profile (MSEP), Functional Outcome of Sleep Questionnaire (FOSQ), Short Form 36 (SF-36) and Epworth Sleepiness Scale (ESS) were completed at the sleep laboratory at baseline and after 6 months of GH replacement therapy.

The MSEP is a questionnaire developed for self-assessment of subtle subjective symptoms perceived by patients.¹⁸ The symptoms included are those previously reported in clinical studies and considered to be primarily related to the central nervous system (CNS). Initially, the MSEP included about 60 items, but as pilot studies showed that many of these were ambiguous or insufficiently sensitive,

the number was finally reduced to only 24. The symptoms were categorized into four groups: 'Contentment', consisting of eight items (Happiness, Tranquility, Self-control, Decisiveness, Responsiveness, Self-confidence, Mental Fatigue, and General Well-being), 'Sleep', consisting of three items (Nocturnal Sleep, Quality of Sleep, and Insomnia), 'Vitality', consisting of five items (Enthusiasm, Initiative, Endurance, Concentration, and Physical Competence) and 'Miscellaneous', consisting of eight items (Dreams, Sexual Interest, Muscular Tension, Numbness, Self-consciousness, Sociability, Appetite, and Sweating). The scale used for recording the symptoms is a visual analogue scale (VAS), e.g. a straight horizontal line, 10 cm in length. The end-points are defined in words denoting the extreme poles of the response to be measured.¹⁹ In all subscales of MSEP, a lower score is consistent with a better QoL.

The FOSQ is a self-administered questionnaire designed to assess the impact of excessive sleepiness on daytime function and to quantify improvement after treatment.²⁰ It contains 30 items divided into five scales: General Productivity, Social Outcome, Activity Level, Vigilance, and Intimacy and Sexual Relationship. A response score of 0 for an item (when an individual does not engage in a particular activity due to reasons other than excessive sleepiness) is coded as a missing response to prevent score bias due to missing answers or skipped questions. Thus, the potential range of scores for any item as well as for the weighted mean item subscale score is 1–4 (from 1 = maximum functional impact to 4 = no functional impact). The number is then transformed to a 100% scale by multiplying the score by 25. Thus, a higher FOSQ subscale is consistent with a better QoL in terms of less or no functional impact of excessive sleepiness on daytime function.

The SF-36 questionnaire was developed as part of a cross-sectional and longitudinal study of variations in health-care practices and outcomes in over 10 000 outpatients.²¹ The SF-36 is self-administered and assesses eight health dimensions, including: (1) physical activities [functioning (PF)]; (2) physical health problems [role (RP)]; (3) bodily pain (BP); (4) general health perceptions (GH); (5) vitality (VT); (6) social activities [functioning (SF)]; (7) emotional problems [role (RE)]; and (8) general mental health (MH). The raw scores for each subscale were transformed to scores that ranged from 0 to 100%, according to the formula: transformed score = [(raw scale score – lowest possible score)/possible score range] × 100%, as recommended.¹⁸ In all subscales of SF-36, a higher score is consistent with a better QoL.

The ESS is an eight-item, self-administered questionnaire used for rating the likelihood of dozing in eight daily situations on a scale of 0–3.²² The final score ranges from 0 (no daytime sleepiness) to 24 (maximum daytime sleepiness).

Biochemical assays

Serum IGF-I concentration was determined by a hydrochloric acid-ethanol extraction radioimmunoassay (RIA) using authentic IGF-I for labelling (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Inter- and intra-assay CVs were 5.4% and 6.9%, respectively, at a mean serum IGF-I concentration of 126 µg/l, and 4.6% and 4.7%, respectively, at a mean serum IGF-I concentration of 327 µg/l. The detection limit of the assay was 13.5 µg/l.

Table 1. Anthropometric, clinical and polysomnographical characteristics of 19 patients (11 men, eight women; mean age 53 years) with GH deficiency (GHD) at baseline and after 6 months of GH replacement therapy

Variable	At baseline	At follow-up	P-value
BMI, kg/m ²	30.5 ± 5.7	30.3 ± 6.0	0.650
WHR	0.96 ± 0.08	0.93 ± 0.03	0.028
GH dose, mg/day	0.14 ± 0.03	0.33 ± 0.11	< 0.001
IGF-I, µg/l	139.7 ± 83.2	224.0 ± 75.7	< 0.001
TST, min	375.1 ± 84.0	375.8 ± 76.2	0.971
Sleep efficiency, %	81.5 ± 14.7	83.7 ± 12.7	0.479
Slow-wave sleep, %	17.8 ± 12.9	18.4 ± 14.0	0.743
REM sleep, %	12.1 ± 6.2	13.9 ± 5.8	0.067
AHI, n/h	28.2 ± 30.0	28.0 ± 31.5	0.933
Non-REM-AHI, n/h	48.0 ± 58.0	52.3 ± 66.2	0.514
REM-AHI, n/h	30.2 ± 28.9	36.6 ± 34.8	0.173
ODI, n/h	18.5 ± 21.8	19.2 ± 26.7	0.821
Sat. min, %	84.5 ± 3.7	82.9 ± 4.2	0.218

*Continuous variables are expressed as mean ± SD, statistics by the paired *t*-test (two-tailed).

BMI, body mass index; WHR, waist hip ratio; TST, total sleep time; REM, rapid eye movement; AHI, apnoea-hypopnoea index; ODI, oxygen desaturation index; Sat. min, minimal oxygen saturation.

Statistics

Continuous variables were expressed as means ± standard deviation (SD) and categorical variables as numbers and proportions (%). An independent Student's *t*-test and the χ^2 -test or Fisher's exact test was applied to compare baseline data between subgroups of GH-deficient patients with vs. without OSA. Comparison of measurements at baseline and 6 months following GH replacement therapy was made by paired *t*-tests in the subgroups, respectively. All the analyses were performed with the Statistical Package for Social Sciences (SPSS, v11.0 for Windows; SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, and a *P*-value less than 0.05 was considered significant.

Results

Table 1 shows that for the whole group, mean BMI was high and remained unchanged while there was a significant decrease in waist-hip ratio (WHR) following 6 months of GH therapy. There were no significant changes in TST and percentage of SWS and REM sleep stages following the GH replacement. Mean AHI was relatively high at baseline and remained unchanged following the GH therapy.

At baseline, OSA was present in 12 GH-deficient patients (63%). There was a trend for patients in the OSA group to be predominantly men, having higher age, BMI and WHR than the non-OSA group (Table 2). The main cause of the GHD in the OSA patients was NFPA (*n* = 10) while two subjects had craniopharyngioma and previous Cushing's syndrome, respectively. The non-OSA group was more heterogeneous and consisted of patients with NFPA (*n* = 2), craniopharyngioma (*n* = 1), Cushing's syndrome (*n* = 1), Rathke's cyst (*n* = 1), hypophysitis (*n* = 1) and prolactinoma (*n* = 1) as the cause of GHD.

Polysomnographically, the OSA group tended to have shorter TST and lower sleep efficiency (SE) than the non-OSA group. The apnoeas

Table 2. Anthropometric, clinical and polysomnographical characteristics of patients with GH deficiency (GHD) without vs. with obstructive sleep apnoea (OSA) at baseline

Variable	Without OSA (n = 7)	With OSA (n = 12)	P-value
Age, years	49.1 ± 13.3	54.7 ± 13.8	0.405
Male gender, n (%)	2 (28.6)	9 (75.0)	0.074
BMI, kg/m ²	29.6 ± 7.2	31.0 ± 4.9	0.619
WHR	0.93 ± 0.09	0.98 ± 0.07	0.176
GH dose, mg/day	0.13 ± 0.03	0.15 ± 0.03	0.097
IGF-I, µg/l	109.4 ± 60.5	157.4 ± 91.7	0.235
TST, min	384.7 ± 65.3	369.5 ± 95.6	0.716
Sleep efficiency, %	86.2 ± 7.4	78.8 ± 17.3	0.302
Slow wave sleep, %	28.6 ± 12.5	11.4 ± 8.1	0.010
REM sleep, %	15.5 ± 3.8	10.1 ± 6.6	0.036
AHI, n/h	3.9 ± 3.0	42.4 ± 29.6	0.003
Non-REM-AHI, n/h	7.9 ± 10.3	71.4 ± 61.8	0.016
REM-AHI, n/h	9.6 ± 9.7	42.3 ± 29.8	0.013
ODI, n/h	2.6 ± 1.9	27.8 ± 22.9	0.011
Sat. min, %	86.4 ± 2.8	83.4 ± 3.8	0.063

*Continuous variables are expressed as mean ± SD, statistics by unpaired Student's *t*-test. Comparison of groups for categorical variables by Fischer's exact test (two-tailed).

BMI, body mass index; WHR, waist hip ratio; TST, total sleep time; REM, rapid eye movement; AHI, apnoea-hypopnoea index; ODI, oxygen desaturation index; Sat. min, minimal oxygen saturation.

and hypopnoeas were more severe and the SWS and REM-sleep time was shorter in the OSA patients than in the non-OSA group (Table 2). All apnoeic and hypopnoeic events were obstructive and observed during REM as well as during non-REM sleep stages. At baseline, there was no difference between the groups regarding MSEP, SF-36, FOSQ and ESS questionnaire scores (data not shown).

In GH-deficient patients without OSA, there was a nonsignificant decrease in BMI (29.6 ± 7.2 vs. 28.9 ± 6.6 kg/m²) and WHR (0.92 ± 0.09 vs. 0.89 ± 0.10) at follow-up. The mean IGF-I level increased from 109.4 µg/l at baseline to 217.9 µg/l following the treatment (*P* = 0.002).

In GH-deficient patients with OSA, there was no change in BMI (31.0 ± 4.9 vs. 31.1 ± 5.7 kg/m²) while WHR decreased (0.98 ± 0.07 vs. 0.95 ± 0.06; *P* = 0.013) at follow-up. The mean IGF-I level increased from 157.4 µg/l at baseline to 227.5 µg/l following the treatment (*P* = 0.010).

As illustrated individually in Fig. 1, there were no significant changes in proportion of SWS time (28.6 ± 12.5% before, 30.2 ± 12.5% after GH) and REM sleep (15.5 ± 3.8% before, 16.0 ± 5.3% after GH) in the non-OSA group. In the GH-deficient patients with concomitant OSA at baseline, the proportion of SWS was almost unchanged (11.4 ± 8.1% vs. 11.6 ± 9.9%) while mean REM-sleep time increased from 10.1 ± 6.6% at baseline to 12.7 ± 6.0% following 6 months of GH replacement therapy (*P* = 0.048).

In the GH-deficient patients without OSA, no significant changes were observed regarding AHI after GH replacement therapy. As illustrated in Fig. 2, two patients (both 65 years old; one man with craniopharyngioma and one woman with NFPA) developed mild sleep apnoea following the treatment. Apnoeic and hypopnoeic events in the whole non-OSA group occurred during both non-REM and REM sleep stages, and all of these events were obstructive. Moreover, no significant changes were observed regarding the ODI as well as minimum oxygen saturation after GH replacement therapy in the GH-deficient patients without OSA at baseline.

Two subjects with OSA at commencement of treatment (a 21-year-old man with NFPA and a 54-year-old woman with previous Cushing's disease) did not fulfil criteria for OSA after 6 months (Fig. 2). For the whole OSA group, there were no significant changes in mean AHI. No changes were observed either regarding the distribution of the obstructive events during non-REM and REM sleep stages, and all of the apnoeas and hypopnoeas were obstructive.

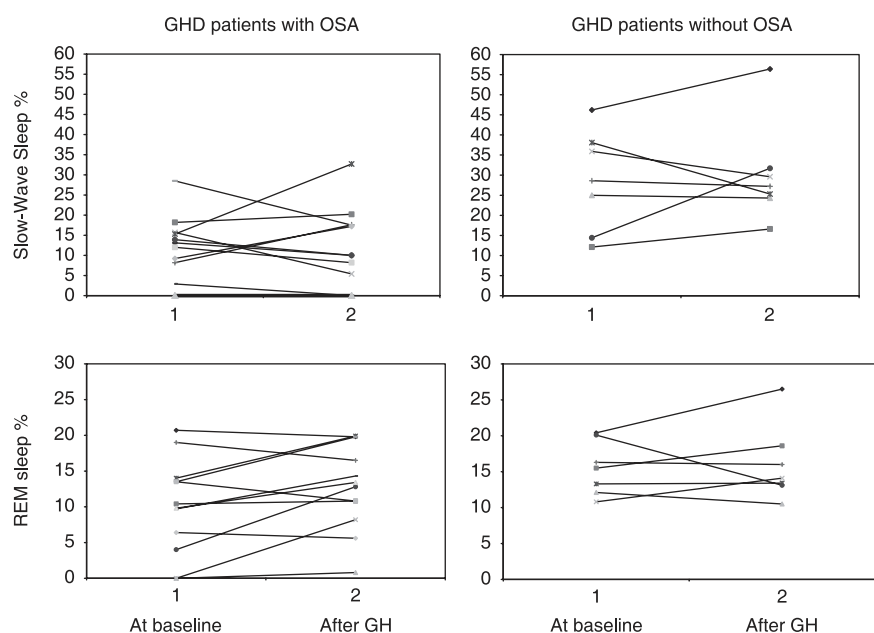


Fig. 1 Proportion of slow-wave sleep and rapid eye movement (REM) sleep time in GH-deficient patients with and without obstructive sleep apnoea (OSA) before and after 6 months of GH replacement therapy (for mean, SD and *P*-values see text).

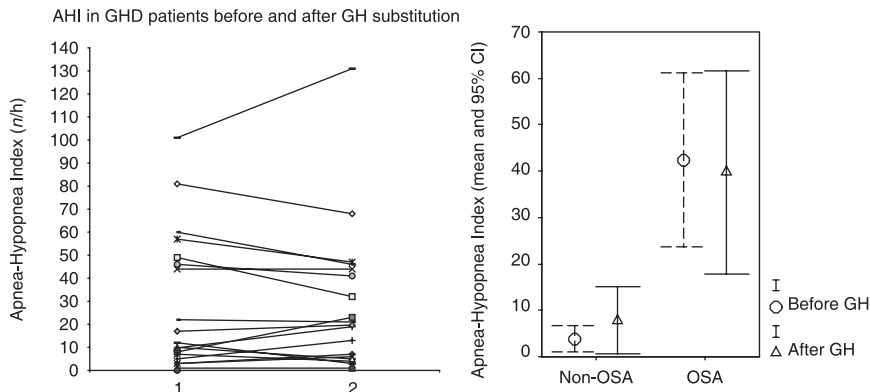


Fig. 2 Changes in the apnoea-hypopnoea index (AHI) individually and in groups before and after 6 months of GH replacement therapy (for P-values see text).

Variables	Without OSA (<i>n</i> = 7)		With OSA (<i>n</i> = 12)	
	Before GH	After GH	Before GH	After GH
FOSQ				
General productivity	87.9 ± 14.7	88.0 ± 14.8	88.5 ± 8.5	94.9 ± 6.2*
Social outcome	91.1 ± 18.7	89.3 ± 19.3	87.5 ± 14.1	92.7 ± 12.5
Activity level	75.1 ± 21.6	70.9 ± 24.5	73.5 ± 13.8	88.0 ± 10.2†
Vigilance	82.0 ± 14.1	90.8 ± 9.3‡	81.5 ± 13.1	90.6 ± 8.8§
IRSA	83.0 ± 18.3	93.8 ± 10.8	80.1 ± 17.0	79.2 ± 20.2
SF-36				
Physical functioning	48.1 ± 17.9	49.1 ± 19.0	52.7 ± 8.8	52.4 ± 15.0
Role, physical	17.9 ± 23.8	28.6 ± 26.7	22.7 ± 24.3	29.6 ± 19.6
Bodily pain	59.4 ± 20.8	58.9 ± 30.8	66.8 ± 15.3	55.7 ± 15.8¶
General health	43.5 ± 18.3	50.4 ± 20.7	41.9 ± 17.4	42.8 ± 12.8
Vitality	35.7 ± 29.5	42.3 ± 29.4	31.3 ± 19.5	49.3 ± 13.2**
Social functioning	61.4 ± 18.7	62.9 ± 23.6	60.0 ± 20.5	63.3 ± 20.2
Role, emotional	26.2 ± 25.2	26.2 ± 25.2	30.6 ± 21.1	34.7 ± 20.7
Mental health	58.6 ± 16.3	60.0 ± 21.1	52.5 ± 12.1	61.9 ± 14.5††
ESS	6.29 ± 6.05	6.57 ± 5.62	7.27 ± 4.20	7.00 ± 4.65

OSA, obstructive sleep apnoea; IRSA, Intimate Relationship and Sexual Activity. Values are means ± SD.

P* = 0.006, †*P* = 0.001, ‡*P* = 0.053, §*P* = 0.032, ¶*P* = 0.009, *P* = 0.002, ††*P* = 0.003.

Neither ODI nor minimum oxygen saturation values were changed significantly following the GH replacement therapy in GH-deficient patients with OSA at baseline.

In all, many dimensions of the MSEP items were slightly improved following 6 months of GH replacement therapy but the changes were statistically significant only in General Well-being (50.7 before vs. 33.1 after GH; *P* = 0.054, in the non-OSA group, and 56.7 before vs. 39.7 after GH; *P* = 0.013, in the OSA group), and in Responsiveness (46.4 before vs. 27.3 after GH; *P* = 0.019) in the OSA patients. Regarding FOSQ scores in the GH-deficient patients without OSA at baseline, an improvement was observed in Vigilance (*P* = 0.053), while other items did not differ significantly after the treatment (Table 3). In the OSA group, there was a significant improvement not only in Vigilance (*P* = 0.032) but also in General Productivity (*P* = 0.006) and in Activity Level (*P* = 0.001). SF-36 questionnaires revealed no significant changes in the non-OSA group while there was an improvement in Vitality (*P* = 0.002) and Mental Health (*P* = 0.003) in the GH-

deficient patients with OSA at baseline (Table 3). However, there was a decline in the SF-36 score due to Bodily Pain (*P* = 0.009) in this group. ESS scores did not change after the treatment period compared with the scores at baseline.

Discussion

Contrary to some previous observations in a smaller group of patients, this study suggests that GH replacement therapy does not induce or aggravate OSA in adults with GHD. Moreover, GH therapy may improve some of the QoL dimensions in these patients.

To our knowledge, this is the first prospective observational investigation of sleep apnoea and its association with GH replacement therapy in an unselected clinical cohort of GH-deficient adults. At baseline, 12 of the 19 GH-deficient adults (63%) had OSA. There was also a trend that the patients in the OSA group were predominantly male, and had higher age, BMI and WHR than the non-OSA group.

These findings suggest that there is a high frequency of OSA in adult GHD and the reason for this could simply be the increased BMI and abdominal obesity. Other possibilities are the multiple neuroendocrine disruptions associated with hypopituitarism and the structural changes in the hypothalamic–pituitary region caused by the underlying disease and its treatment. This latter possibility is less likely as there was no clustering of patients in the OSA group with craniopharyngiomas and other diseases associated with more hypothalamic problems. In addition, the obstructive nature of the apnoeas suggests that obesity possibly associated with endocrine status is the major cause of increased OSA in this population.

Several previous studies suggest increased cardiovascular morbidity and mortality in hypopituitary patients without GH replacement therapy.^{23–27} The mechanisms related to increased cardiovascular morbidity in OSA patients have been discussed in detail elsewhere.²⁸ Repeated nocturnal hypoxaemia,²⁹ as well as sympathetic activation,³⁰ disturbed endothelial function³¹ and increased vasoconstrictor sensitivity to angiotensin II,³² are some of the proposed mediating mechanisms. The high prevalence of OSA in hypopituitary adults might be an important link in this context because of the previously reported endothelial dysfunction,³³ sympathoexcitation³⁴ and their increased mortality.

Our results confirm findings from a recent study showing no changes in sleep architecture after 6 months of GH replacement therapy.⁸ However, our results from the OSA group also support the previous report of increased REM sleep in subjects with GHD.⁷ The marginal increase in REM sleep in the OSA group in our cohort should be interpreted cautiously as it may be attributed to the regression towards the mean phenomenon. It should also be noted that our protocol did not contain a night of polysomnography acclimatization. It is possible that sleep measures such as sleep latency and TST were systematically changed due to a first-night effect. Although less likely, this may also have been the case for the relative content of SWS and REM sleep in the recorded sleep periods.

Previous studies have not reported on the presence of OSA, a confounding variable when studying sleep architecture explaining some of the contrasting reports in the literature. GHD and also GH replacement have also been reported to affect OSA. A new onset of severe OSA was reported in a man during GH replacement therapy, and a consequent study of five middle-aged men with GHD from the same clinic revealed that cessation of GH replacement therapy was associated with a decrease in SWS and a shift from obstructive to central apnoea and hypopnoea.¹¹ The GH dose used in that study (median dose 0.66 mg/day, range 0.66–1.3 mg/day) was double the dose used in our study (Table 1). Moreover, in our sample, two GH-deficient patients developed mild OSA, whereas two patients with OSA at baseline were free of OSA 6 months after the GH replacement therapy.

Thus, our results do not suggest any increased risk for OSA during GH replacement in GH-deficient adults in the short term. By contrast, acromegalic patients with GH excess have a high prevalence of SDB (both central and obstructive apnoeas),⁹ and reduction of GH levels by octreotide treatment reduced their SDB.¹⁰ Therefore, the effect of GH replacement therapy in GH-deficient adults is very different from that observed in untreated acromegaly. The most plausible explanation for this difference is the long-standing markedly excessive GH and serum IGF-I levels in acromegaly, often accompanied

by severe soft-tissue swelling and enlargement affecting the upper airways and tongue. In GHD, however, the clinical features are characterized by reduced hydration of the soft tissue, and treatment results in normalization. Other factors predisposing to OSA in GH-deficient patients might also be related to the type of previous surgery, that is transfrontal vs. transsphenoidal, as the latter often gives rise to nasopharyngeal problems. In our study, nine patients with OSA had previously been treated with transsphenoidal surgery, which may support this possibility. These entities remain to be addressed in further studies.

Although the total number of GH-deficient patients without OSA was low in this study, it is noteworthy that these were the subjects with normal SWS and REM time during sleep. Thus, our data clearly indicate that OSA is the main contributing factor to shorter SWS and REM sleep in adults with GHD. After 6 months of GH replacement, however, an improvement in REM sleep was only observed in the GH-deficient patients with OSA. As discussed above, an effect of the regression to the mean is possible, but this is in line with the effects of GH replacement on several other variables. An inverse relationship between the responsiveness to GH replacement therapy and the baseline status has previously also been found for muscle strength,³⁵ bone mass and density³⁶ and serum lipid pattern.³⁷

As only a few subjects were regarded as 'nonresponders' in this study cohort, the present data are not sufficient to determine whether there is an association between nonresponding GHD and a concomitant OSA. As both OSA and non-OSA groups of the GH-deficient cohort had similar QoL measures at baseline, OSA alone could not explain the low QoL in GHD. However, the clinical response, in terms of improved well-being and some other QoL dimensions in GHD with concomitant OSA, suggests a favourable impact of GH substitution in these patients. Whether this improvement is a result of the small changes in the sleep architecture is difficult to know because of the small number of patients in the study. It does, however, suggest that other mechanisms are more likely, such as the direct effects of GH and IGF-I on the brain.³⁸

The high prevalence of OSA in a consecutive sample of GH-deficient adults highlights an additional explanation for some cardiovascular observations and increased cardiovascular morbidity and mortality in these subjects. It should also be kept in mind that there has been some scepticism about GH replacement as it has been suggested to induce severe OSA in GH-deficient adults.¹¹ Our study clearly suggests that this is not a major concern if appropriate GH replacement is performed. Indeed, there was a beneficial effect in terms of a reduction in WHR, an increase in the proportion of REM sleep and also improvement in some of the QoL dimensions. The recognition of OSA and specific treatment with CPAP or other modalities could contribute to a further improvement in QoL and cardiovascular status of adults with GHD.

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