NEW RESEARCH

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Increased Neck Soft Tissue Mass and Worsening of Obstructive Sleep Apnea after Growth Hormone Treatment in Men with Abdominal Obesity

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Background: Risk factors for obstructive sleep apnea (OSA) are male gender, obesity and abnormalities in neck soft tissue mass. OSA is associated with both growth hormone (GH) excess and severe GH deficiency in adults. Adults with abdominal obesity have markedly suppressed GH secretion.

Aim: To study the effect of GH treatment on OSA in abdominally obese men with impaired glucose tolerance.

Patients and Methods: Forty men with abdominal obesity and glucose intolerance were randomized in a prospective, 12-month double-blind trial to receive either GH or placebo. The treatment groups had similar BMI and waist circumference. Overnight polysomnography and computed tomography to assess muscle and fat distribution in the neck and abdomen were performed at baseline and after 12 months.

Results: GH treatment increased insulin-like growth-factor-1 from (mean [SD]) 168 (72) to 292 (117) µg/L, the apnea-hypopnea index from (n/h) 31 (20) to 43 (25) and oxygen-desaturation index from (n/h) 18 (14) to 29 (21) (p = 0.0001, 0.001, 0.002). Neck transverse diameter, circumference and total cross-sectional area (p = 0.007, 0.01, 0.02) increased, while abdominal visceral adipose tissue (p = 0.007) was reduced. No between-group differences in total sleep time, REM sleep, NREM sleep, and time spent in supine position were found. The Epworth sleepiness scale score was unchanged.

Conclusions: GH treatment increased the severity of OSA in abdominally obese men. The possible mechanism appears to be reflected by the GH-induced increase of measures of neck volume. The present results, to some extent, argue against that low GH/IGF-I activity is a primary cause of OSA in abdominally obese men.

Keywords: Growth hormone treatment; obstructive sleep apnea; abdominal obesity, GH-IGF-1 axis

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SCIENTIFIC INVESTIGATIONS

Obstructive sleep apnea (OSA) is a sleep related breathing disorder associated with increased cardiovascular morbidity.[1] It is characterized by a recurrent occlusion of the upper airways during sleep, resulting in hypoxia and asphyxia.[1] The relationship between OSA and abnormalities in the growth hormone (GH)-insulin-like growth factor (IGF)-1 axis is intricate. In states of GH overproduction, such as acromegaly, the increased occurrence of OSA is associated with anatomical narrowing of the pharyngeal lumen[2,3] and craniofacial changes.[4] Reduced activity in the GH-IGF-1 axis is also associated with OSA, particularly in obese individuals,[5-7] which can be partly restored by treatment of the OSA by continuous positive airway pressure.[6] Furthermore, pulsatile GH secretion is impaired in patients with disturbed sleep architecture and decreased slow wave sleep.[8,9]

Abnormalities in the upper airway soft tissue anatomy may play a role in the pathogenesis of OSA in obese individuals.[10] Neck circumference (NC) shows a better correlation than BMI with apnea severity, suggesting that fat deposition in the neck may be involved in the pathogenesis of OSA.[10,11] Other causes of increased neck circumference include increased overnight fluid displacement from the legs to the neck during sleep induced by a recumbent position particularly in individuals with a sedentary way of life.[12]

On the other hand, recent data suggest that there is a strong link between OSA and abdominal obesity and the clustering of metabolic abnormalities that characterize the metabolic syndrome.[13] Based on the knowledge that OSA is a common

BRIEF SUMMARY

Current Knowledge/Study Rationale: The present study aimed to investigate the effect of GH treatment on OSA severity, sleep architecture and soft tissue mass and distribution in the neck in men with abdominal obesity and glucose intolerance.

Study Impact: This study suggests that obstructive sleep apnoea severity is increased with growth hormone treatment. One possible mechanism appears to be reflected by the GH-induced increase of measures of neck volume.

feature in active acromegaly, there is concern that GH therapy may induce OSA. However, severe sleep apnea has also been reported in 5 men with hypopituitarism 6 months after the cessation of GH replacement therapy.[14] In addition, there are studies demonstrating that 6 months' treatment with GH in severely GH-deficient patients did not induce or aggravate OSA.[15] GH supplementation in patients with Prader-Willi syndrome (PWS), a genetic disorder associated with morbid obesity and a high prevalence of OSA and other types of sleep disordered breathing (SDB) has demonstrated favorable effects on growth, body composition,[16] and other metabolic risk factors of CVD.[17] In abdominally obese middle-aged men, long-term GH treatment has been shown to be effective in reducing abdominal fat accumulation and improving the lipid profile and diastolic pressure.[18] However, it is not known whether GH treatment exerts any effect on sleep-related breathing disorders in individuals with abdominal obesity and other features of the metabolic syndrome. To our knowledge, the effect of GH on adipose tissue distribution in the neck has not yet been studied.

This randomized, placebo-controlled trial in abdominally obese men was originally designed to address the metabolic effect of long-term growth hormone treatment. The protocol was expanded to include the effects on obstructive sleep apnea indices as well as the relationship between OSA and possible alterations of the distribution of fat and lean mass in the neck.

METHODS

Subjects

Forty men aged 40-65 years with abdominal obesity and glucose intolerance, were eligible for the study. They were recruited by advertisements in a local newspaper. The inclusion criteria were a waist/hip ratio (WHR) > 0.95, BMI of > 25 kg/m^2, an impaired fasting glucose (IFG): fasting plasma glucose level ≥ 6.1 and ≤ 7.8 mmol/L and/or impaired glucose tolerance (IGT) defined as a plasma glucose level 2 hours after a 75 g oral glucose load (oral glucose tolerance test, OGTT) of between 6.9-11.0 mmol/L. Patients with proliferative diabetic retinopathy, macro-albuminuria and/or serum creatinine > 150 mmol/L, known ischemic heart disease, previous stroke or intermittent claudication, known malignancy, or other hormonal therapy were excluded from the study.

Ethical Considerations

All patients received verbal information, and written informed consent form was signed and dated by the patients before entering the study. The study was conducted according to the Helsinki Declaration and according to the Good Clinical Practice Program, produced by the International Conference on Harmonization and approved by the local ethics committee.

Study Design

This was a prospective, randomized, double-blind, placebo-controlled study with a run-in period of one month to achieve stable conventional treatment for hypertension and so on, before randomization to treatment groups. An overnight sleep recording, computed tomography (CT) to assess muscle and fat distribution in the neck and the abdomen and glucose metabolism were assessed before the start and after 12 months of treatment. Physical and laboratory examinations including safety assessments were performed at the start and after 1, 2, 3, 6, 9, and 12 months. Body weight (BW) was measured in the morning to the nearest 0.1 kg using a calibrated scale. Body height was measured barefoot to the nearest 0.01 m. The body mass index (BMI) was calculated as BW in kg divided by height in meters squared. Measuring waist circumference in the standing position with a flexible plastic tape midway between the lower rib margin and the iliac crest assessed body composition. The sagittal abdominal diameter was also measured using a digital sagittalometer with a fixed ruler (an in-house design). The height from a firm bed to the highest point of the abdomen was measured in the supine position at the level of the iliac crest. The within-patient variation between two measurements was 0.2 mm.

Systolic and diastolic blood pressures were measured after 5 minutes' supine rest with an automatic sphygmomanometer. The mean of 3 measurements with a one-minute interval in between was used for evaluation.

Treatment

Patients were randomized to either a recombinant human GH (Genotropin, Pfizer) group or a placebo treatment group. Both groups were matched in terms of BMI and waist circumference at baseline. GH was administered daily as a subcutaneous injection before bedtime with an initial dose of 0.13 mg/day. After 2 and 4 weeks of treatment, the dose was increased to 0.27 mg/day and 0.40 mg/day, respectively, to reach the target dose of 0.53 mg/day after 6 weeks of treatment. In the event of side-effects, the dose was reduced by half. Oral and written instructions relating to administration and dose were given.

The patients were asked to have a stable dietary intake (more than 150 g of carbohydrate/day) and normal physical activity on 3 consecutive days prior to study days. The patients were asked to refrain from tobacco in any form after 20:00 on the evening prior to study participation. During the study, all the subjects continued a diet regimen and visited a dietician every 3 months.

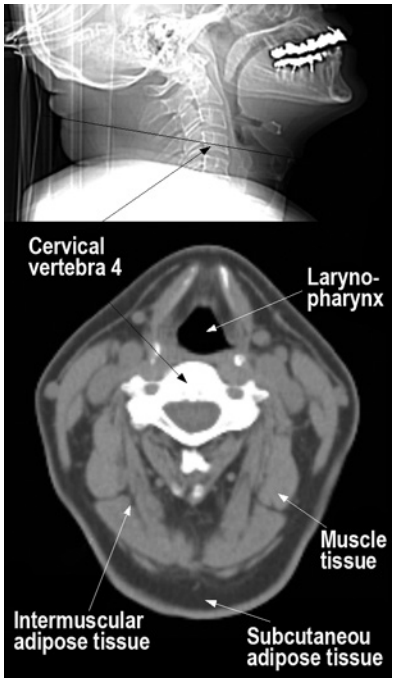
Polysomnography

A full-night polysomnographic (PSG) sleep recording was made at baseline and before ending treatment, using the EMBLA (Embla, A10, Flaga, Reykjavik, Iceland) ambulatory PSG system. A 12-channel montage was used as follows; 4-channel electroencephalography (EEG; C3-A2, C4-A1, O1-A2, O2-A1), 2-channel electrooculography (EOG; EOG-L, EOG-R), 1-channel submental electromyography (EMG), tibial EMG, oxygen saturation using pulse oximetry, thoraco-abdominal effort belts (movement detection), nasal and oral air flow (thermistor), and pressure and body position recorder.

All recordings were scored according to Rechtschaffen and Kales criteria.[19] Obstructive sleep apneas were distinguished from central apneas. Events detected in this trial were almost exclusively of obstructive type.

Obstructive sleep apnea events were defined as > 90% drop in the peak of the thermistor airflow from baseline lasting ≥ 10 sec with continued or increased inspiratory effort throughout the entire period of absent airflow. A hypopnea was defined as a

Figure 1



Top—Sagittal image showing the level of the neck CT scan, in the fourth cervical vertebra and parallel to the third and fourth cervical intervertebral space. **Bottom**—Cross-sectional area showing laryngo-pharynx, muscle tissue area, subcutaneous adipose tissue (SAT) area and intermuscular adipose tissue (IMAT) area.

thermal signal drop of 30% to ≥ 50% of baseline with duration > 10 sec, accompanied by respiratory effort and by either desaturation ≥ 3% or an arousal. The apnea-hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of sleep (n/h), and OSA was defined as an AHI ≥ 10/h. The oxygen desaturation index (ODI) was based on a 4% desaturation from baseline and was calculated as the number of significant desaturations per hour of sleep; and the minimum oxygen saturation ($MinO_2Sat$) during the overnight recording was determined.

Subjective Sleepiness Questionnaire

The Epworth Sleepiness Scale (ESS) was administered at baseline and after 12 months. It is an instrument employed in sleep apnea research to measure subjective perceptions of falling asleep during different daytime activities.[20]

Short Form-36

The short form-36 (SF-36) is a self-administered questionnaire that assesses 8 health dimensions.[21]

Functional Outcome of Sleep Questionnaire

The functional outcome of sleep questionnaire (FOSQ) is a self-administered questionnaire designed to assess the impact of excessive sleepiness and daytime function and to quantify improvement after treatment.[22]

Body Composition Assessment

Regional body adipose tissue and muscle tissue measurements were assessed with computed tomography (CT). A single-slice system, HiSpeed Advantage version RP2 (GE Medical Systems, Milwaukee, WI, USA), was used. The scanning protocol included one scout for localizing the neck image (**Figure 1** top). The axial image (**Figure 1** bottom) was positioned in the fourth cervical vertebra and parallel to the intervertebral space between the third and fourth cervical vertebrae. Since this angle differed between subjects, the magnitude of measurement values was recalculated with an algorithm to correspond to the transverse plane. The level of the fourth lumbar vertebra was chosen for measuring abdominal adipose tissue. A second scout was used to position an axial image at the middle of the fourth lumbar vertebra.

The outer contours of the neck and the trunk were calculated automatically. The transverse diameter of the neck was determined as the maximum horizontal distance of the neck contour. The area of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) was calculated as the difference between the total area of adipose tissue (AT) and the area of adipose tissue inside a contour manually drawn in muscle tissue, or in some locations bone tissue, just inside the subcutaneous adipose tissue. The adipose tissue area within a contour was calculated as the summed area of all pixels on and inside the contour within the attenuation range -190 Hounsfield units (HU) to -30 HU.[23] Intermuscular adipose tissue (IMAT) area was calculated as the difference between the adipose tissue area within the contour in the outer part of the muscle and the adipose tissue area within a corresponding contour manually drawn in the inner part of the muscle tissue. Visceral adipose tissue area was measured inside a manually drawn contour just outside the intraabdominal space, using the attenuation range for adipose tissue. Muscle tissue area was calculated using a contour manually drawn just outside the muscle. Pixels with attenuation values ranging from -29 HU to 150 HU were included in the muscle tissue area.[23]

At the end of treatment examination, the original scouts were displayed next to the CT display monitor, with the position of the axial images shown for guidance to achieve the same position. The CT protocol was optimized with regard to body composition assessment and low radiation dose. Patient-specific scan parameters were chosen according to the transverse diameter of each anatomical section.[24] The effective radiation dose per examination was < 0.8 mSv.

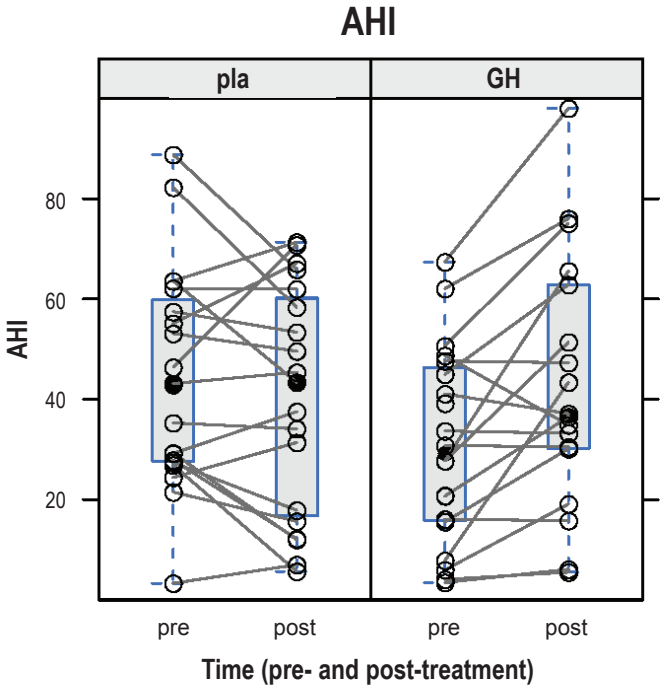
Biochemical Assay

Blood samples were collected in the morning after an overnight fast. The samples were frozen at -80ºC until assay. Serum IGF-I concentration was determined by radioimmunoassay (RIA) after HCl/ethanol precipitation of binding proteins (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The standard deviation (SD) score for IGF-I was calculated from the predicted IGF-I values, adjusted for age and sex values obtained from the normal population.[25] Serum insulin was determined by RIA (Pharmacia, Uppsala, Sweden), and plasma glucose was measured by the Gluco-quant method (Roche/Hitachi, Mannheim, Germany).

Insulin Sensitivity Measurements

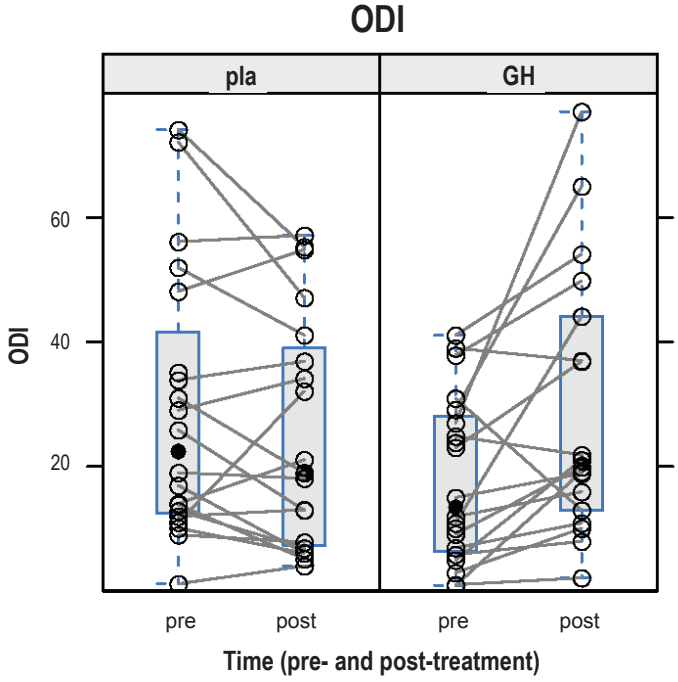
The homeostasis assessment model (HOMA) was used to determine insulin resistance (IR). A higher HOMA-IR value

Figure 2—Boxplot of AHI pre- and post- GH or placebo (pla) treatment, indicating the lower and upper quartiles (25% and 75%) with the central line indicating the median.



The length of the whiskers shows the range to the 2.5% and 97.5% percentiles.

Figure 3—Boxplots of ODI pre- and post- GH or placebo (pla) treatment.



indicates a higher insulin resistance and is calculated using the following equation: fasting plasma insulin × fasting plasma glucose/22.5. The β-cell function was assessed using the β-cell function index; ((20 × fasting insulin)/(fasting glucose-3, 5))/100.[26]

Statistical Analysis

All the analyses were performed with R statistical language (version 2.6.1) using the NLME library. The effects of GH on response variables (e.g., AHI and BMI) were examined using a linear mixed effects regression model with fixed effects of treatment group and time and their interaction. Post hoc contrasts were calculated using the Welch 2-sample *t*-test. The data are presented as the mean (SD) and 95% confidence intervals. A 2-tailed p-value ≤ 0.05 was considered significant. The ordinal scaled Epworth Sleepiness Scale and the subjective questionnaires were analyzed using a Kruskal-Wallis nonparametric ANOVA.

RESULTS

Forty subjects were initially randomized to either the GH treatment group or the placebo-treated group. The mean maintenance GH dose was 0.51 mg/day (0.27-0.53 mg/day) and was well tolerated. Two GH-treated individuals exhibited mild symptoms of fluid retention that subsided after a reduction of the dose. In the GH-treated group there were 2 dropouts, one because of edema and one due to depression (n = 18). In the placebo-treated group, one dropout occurred due to personal reasons (n = 19). Individuals who did not complete the 12-month treatment were excluded from all statistical analyses.

Both groups were similar in terms of baseline BMI, waist circumference, sagittal diameter and systolic and diastolic blood pressure. No changes were observed neither in HOMA-IR, β-cell function index, anthropometric measures nor clinical variables (**Table 1**) after 12 months. A weight difference was observed between the groups at baseline (**Table 1**).

After 12 months of GH-treatment the IGF-1 increased from 168 (71.8) µg/L at baseline to 292 (116.8) µg/L (group * time interaction $F_{1,35}$ = 33, p = < 0.0001). Serum IGF-1 score increased from -0.25 SD at baseline to 2.4 SD in the GH-treated group (interaction $F_{1,35}$ = 33, p = 0.0001) and in the placebo group the IGF-1 score was unchanged after 12 months (-0.25 SD at baseline and -0.2 SD after 12 months, p = 0.5).

Polysomnographic Characteristics and Sleep Architecture

After 12 months of GH treatment AHI increased by approximately 12 events per hour (group * time interaction $F_{1,35}$ = 12, 95% CI = 4.5, 19.5, p = 0.001) (**Figure 2**) and ODI increased by 4 events per hour ($F_{1,35}$ = 11, 95% CI = -17.8, 25.8, p = 0.002) (**Figure 3**), with no changes in the placebo group. The MinO$_2$Sat did not change in the GH-treated group as compared to the placebo group (p = 0.3) (**Table 2**). The increase that occurred in the AHI was seen mainly during NREM sleep (interaction $F_{1,35}$ = 10, mean$_{95\%\ CI}$ = $_{15.8}$15.5$_{26.5}$, p = 0.003) (**Table 2**). No sig-

Table 1—Anthropometric measures and clinical characteristics at baseline and after 12 months in the GH group and the placebo group.

Variables	Treatment	Baseline	12 months	p-value[a]
Age (years, range)	GH	61 (50-73)	61 (50-73)	0.1
	Placebo	65 (48-74)	65 (48-74)	
BMI (kg/m^2)	GH	31 (3.3)	31 (3.1)	0.6
	Placebo	32 (2.8)	32 (2.9)	
Weight (kg)	GH	98 (12.2)[b]	99 (11.5)	0.3
	Placebo	100 (12.8)	100 (12.9)	
Waist circumference (cm)	GH	110 (8.3)	109 (7.4)	0.4
	Placebo	114 (8.3)	112 (8.8)	
Abdominal sagittal diameter (cm)	GH	27 (2.6)	26 (2.0)	0.08
	Placebo	27 (2.2)	28 (2.4)	
Systolic BP (mm Hg)	GH	133 (12.3)	135 (14.6)	0.2
	Placebo	138 (11.4)	135 (13.2)	
Diastolic BP (mm Hg)	GH	82 (8.9)	83 (10.2)	0.5
	Placebo	82 (6.7)	81 (7.3)	
IGF-1 (µg/L)	GH	168 (71.8)	292 (116.8)	0.0001
	Placebo	160 (31.3)	160 (26.4)	

Variables are expressed as the mean (SD), with [a]p-value for treatment and time interaction from linear mixed effects regression models. [b]p-value ≤ 0.02, Welch unpaired *t*-test between groups at baseline.
BMI refers to body mass index; BP, blood pressure; IGF-1, insulin-like growth factor-1.

nificant between-group changes were seen in mean total sleep time (TST), REM sleep time (REM-T), slow wave sleep time (SWS-T), sleep efficiency (SE), or sleep latency (SL) after 12 months (**Table 2**).

Neck and Abdominal Fat and Muscle Distribution

After 12 months of GH treatment, neck transverse diameter (**Figure 4**), neck circumference and neck total cross-sectional area increased (interaction $F_{1,35} = 7$, mean $_{95\%\ CI} = {}_{0.1}0.5_{0.91}$ cm, p = 0.007, $F_{1,35} = 7$, mean$_{95\%\ CI} = {}_{0.2}1.1_{2.0}$ cm, p = 0.01, $F_{1,35} = 6$, mean $_{95\%\ CI} = {}_{1.3}7.1_{13.1}$ cm^2, p = 0.02 respectively) compared with the placebo group (**Table 3**).

GH treatment tended to increase neck muscle area (interaction $F_{1,35} = 3$, mean $_{95\%\ CI} = {}_{-0.9}\ 9.8\ {}_{20.5}$ cm^2, p = 0.07), whereas no differences were seen between the GH/placebo groups in terms of neck subcutaneous adipose tissue area (SAT) or neck intermuscular adipose tissue area (IMAT) (**Table 3**). Treatment related effects on AHI and on neck transverse diameter and neck circumference were not related to each other. Abdominal visceral adipose tissue (VAT) decreased by 26 cm^2 after 12 months of GH treatment (interaction $F_{1,35} = 8$, mean $_{95\%\ CI} = {}_{8.1}26_{42.8}$ cm^2, p = 0.007), while no changes were apparent in the placebo group. Abdominal subcutaneous adipose tissue (SAT) was not affected by 12 months of GH treatment (**Table 3**).

Daytime Sleepiness and Quality of Life Questionnaires

Neither the ESS score, the SF-36 nor the FOSQ score was significantly changed by treatment in the 12 months assessments (p = 0.5, p = 0.8, p = 0.8, respectively).

Table 2—Polysomnographic characteristics, clinical and subjective changes at baseline and after 12 months in the GH group and the placebo group

Variables	Treatment	Baseline	12 months	p-value[a]
AHI (n/h)	GH	31 (20.0)[b]	43 (25.2)	0.001
	Placebo	44 (22.2)	40 (23.0)	
ODI (n/h)	GH	18 (13.8)[b]	29 (21.3)	0.002
	Placebo	29 (21.9)	25 (18.9)	
MinO_2Sat	GH	84 (3.6)[b]	81 (5.2)	0.3
	Placebo	79 (7.8)	78 (6.9)	
REM-AHI (n/h)	GH	35 (27.6)[b]	46 (24.0)	0.3
	Placebo	51 (24.3)	55 (23.3)	
NREM-AHI (n/h)	GH	29 (19.7)	41 (26.9)	0.003
	Placebo	42 (24.1)	38 (23.6)	
Total sleep time (min)	GH	399 (54.4)	404 (77.7)	0.4
	Placebo	373 (79.7)	413 (52.3)	
REM-T (min)	GH	50 (30.6)	54 (35.7)	0.8
	Placebo	51 (31.1)	53 (31.1)	
NREM-T (min)	GH	348 (49.1)	360 (47.1)	0.4
	Placebo	323 (61.8)	350 (54.7)	
SWS-T (min)	GH	45 (30.1)	40 (31.1)	0.9
	Placebo	44 (34.7)	40 (32.5)	
Sleep efficiency (%)	GH	87 (5.2)	86 (8.3)	0.3
	Placebo	87 (5.5)	83 (13.4)	
Sleep latency (%)	GH	15 (12.8)	16 (14.0)	0.6
	Placebo	18 (12.5)	16 (17.4)	
Supine position (min)	GH	112 (101.2)	122 (102.3)	0.8
	Placebo	129 (100.5)	133 (142.2)	

Variables are expressed as the mean (SD), with [a]p-value for treatment and time interaction from linear mixed effects regression models. [b]p-value ≤ 0.05, Welch unpaired *t*-test between groups at baseline.
AHI refers to apnea-hypopnea index; ODI, oxygen desaturation index; MinO_2Sat, minimum oxygen saturation; REM-T, rapid eye movement sleep time; NREM-T, non-rapid eye movement sleep time; SWS-T, slow wave sleep time.

DISCUSSION

The present study aimed to investigate the effect of GH treatment on OSA severity, sleep architecture and soft tissue mass and distribution in the neck in men with abdominal obesity and glucose intolerance. OSA was a frequent finding and its severity in the GH-treated group increased, together with an increase in neck transverse diameter, neck circumference and total neck cross-sectional area. Sleep architecture, as well as the subjective perception of daytime sleepiness, was not affected by GH treatment.

To our knowledge, this is the first prospective, placebo-controlled trial investigating the effect of GH on fat and muscle distribution in the neck in individuals with a high prevalence of OSA. Since the diagnosis of OSA was not an inclusion criterion, large variability in terms of the occurrence and severity of OSA indices and TST was observed within and between the groups. At baseline, 13 GH-treated men (72%) and 18 placebo-treated men (95%) were found to have OSA. After 12 months of GH treatment, there was a 32% increase in AHI and a 63% increase

Figure 4—Boxplots of neck transverse diameter pre- and post- GH or placebo (pla) treatment.

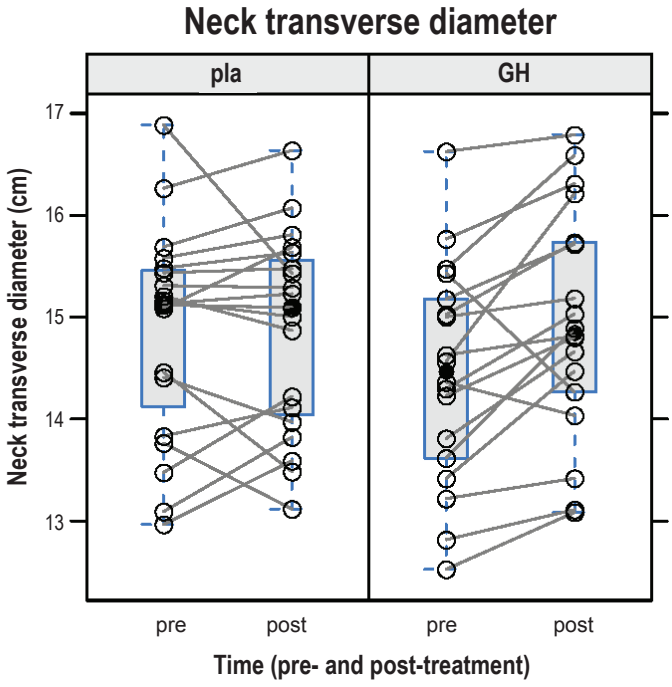


Table 3—Neck (level at 4th cervical vertebra) and abdominal (level at 4th lumbar vertebra) measurements by computed tomography

Variables	Treatment	Baseline	12 months	p-value
Neck circumference (cm)	GH	47 (2.6)	48 (2.6)	0.01
	Placebo	48 (2.7)	48 (2.8)	
Neck total cross-sectional area (cm^2)	GH	172 (20.5)	179 (19.6)	0.02
	Placebo	179 (19.5)	179 (20.9)	
Neck transverse diameter (cm)	GH	14 (1.1)	15 (1.1)	0.007
	Placebo	15 (1.0)	15 (1.0)	
Neck muscle area (cm^2)	GH	84 (22.6)	93 (11.5)	0.07
	Placebo	91 (12.9)	90 (12.5)	
Neck subcutaneous adipose tissue area (cm^2)	GH	35 (10.9)	37 (10.8)	1.0
	Placebo	37 (12.7)	39 (13.1)	
Neck intermuscular adipose tissue area (cm^2)	GH	22 (6.4)	23 (6.0)	0.7
	Placebo	23 (5.4)	24 (6.3)	
Abdominal visceral adipose tissue (cm^2)	GH	230 (71.7)	208 (64.4)	0.007
	Placebo	234 (89.8)	238 (90.2)	
Abdominal subcutaneous adipose tissue (cm^2)	GH	301 (103.9)	300 (89.9)	0.9
	Placebo	310 (100.3)	308 (101.4)	

Variables are expressed as the mean (SD), with p-value for treatment and time interaction from linear mixed effects regression models.

in ODI; while daytime sleepiness, REM sleep, TST, and SWS were unaffected. The baseline differences in the frequency and severity of the OSA indices among the two study groups is not likely to explain the deterioration in the GH-treated group. This conclusion is drawn from analyzing the individual data showing that the deterioration was apparent in the GH-treated men with baseline values comparable to those men in the placebo group who did not demonstrate any changes in their OSA indices (**Figures 2** and **3**). The deterioration of OSA could neither be explained by an association with supine position when comparing both groups at baseline and after 12 months.

The mean maintenance dose of GH was 0.51 mg/day. This dose produced a mean serum IGF-1 score of 2.4 SD in the GH-treated group, suggesting that the dose of GH was slightly supra-physiological. This could possibly have influenced the outcome in terms of the severity of OSA indexes.

Several previous studies have pointed to neck size as an arbitrary measure of sleep apnea severity.[27] Other data suggest that the local accumulation of fat in fat pads adjacent to the lateral walls of the pharynx[28,29] may affect upper airway patency and predispose to OSA. Other data[30] suggest that changes in neck lean tissue could also have an important effect on OSA. Little is as yet known about the effect of GH on body composition in the neck. We hypothesized that GH, through its lipolytic effect, could reduce the amount of fat mass in the neck and thereby reduce the severity of OSA. In the present study, the CT measurements showed significant increases in neck circumference, transverse diameter and total cross-sectional area and a tendency towards increased neck muscle area ($p = 0.07$), whereas neck adipose areas were unchanged. The combined increase in extracellular water and muscle mass induced by GH[31] and the failure of GH to reduce fat mass in the neck could explain the increase in soft tissue volume in the neck. The unchanged neck adipose tissue in response to GH further supports the depot-specific effects of GH.[32]

Total body water was not measured in the current study but there is recent data suggesting that a rostral shift of tissue fluid as a result of the intake of the overnight supine position may contribute to the occurrence of apneas.[12] It cannot be excluded that the extent of such fluid shifts may have been affected by long term GH treatment.

One important limitation in this study is that the applied CT methodology did not visualize the anatomical structures in the immediate parapharyngeal region, an area regarded as particularly important for the development of OSA.[30,33,34]

However a direct relationship between OSA severity and increase in neck transverse diameter is indirectly supported by previous CT data, which link an enlargement of the soft tissue structures surrounding the upper airways to a lateral narrowing of the airways.[30] We therefore propose that the increased neck diameter following GH administration led to an increase in the severity of OSA. This may have been particularly evident in subjects with a pre-existing reduction in the patency of the airways reflecting an increase in the critical collapsing pressure.[34]

The prevalence of OSA increases among patients with severe GH deficiency[15] and in patients with acromegaly, a condition with longstanding GH excess.[35] One possible explanation for this contrasting association is that patients with both deficiency and excess have increased body and tissue size (in GH deficiency due to increased fat mass and in acromegaly due to a combination of an increase in lean body mass and skeletal abnormalities).[4]

Increased intra-abdominal fat accumulation, sympathetic nerve activity, and insulin resistance have been associated with

OSA.[13] However, BMI, waist circumference, and abdominal sagittal diameter and subcutaneous adipose tissue were unaffected by GH treatment and are thus unlikely to have influenced the change in OSA severity seen in the treatment group.[36] Abdominal visceral adipose tissue decreased after 12 months of GH treatment and it seems unlikely that the deterioration of OSA was affected by this change. It also seems unlikely that a change in insulin sensitivity contributed to the GH-induced deterioration in OSA, as no changes were observed in the studied markers of glucose tolerance and insulin sensitivity. The deterioration in OSA indexes as a result of GH in this study but not in a previous study[15] of patients with severe GH deficiency due to hypothalamic-pituitary disease may reflect a dose dependency or else the more marked baseline GH deficiency in such patients could possibly explain a more favorable outcome in terms of OSA. Reduced GH/IGF-I activity has been associated with OSA in obese individuals[5-7] and can be partly restored by treatment with continuous positive airway pressure.[6] However, the lack of beneficial effect of GH treatment in this study argues against, at least to some extent, that reduced GH/IGF-I activity provides a dominant etiological factor behind OSA development in obese individuals.

The 12-month GH treatment had no effect on measures of sleep architecture. In GH-deficient adults, GH administration increased REM sleep in some[37,38] but not in all[39] previous studies. It is therefore possible, as discussed above for OSA indexes, that the effect of GH on sleep architecture is less marked in abdominally obese subjects as compared with that in GH-deficient adults.

The subjective perception of daytime sleepiness, assessed by the ESS questionnaire, was unchanged by the GH treatment. As a result, the GH-induced deterioration in the AHI and ODI indexes was asymptomatic in terms of daytime sleepiness. A deterioration in OSA as a result of GH treatment could, however, increase the cardiovascular risk in the abdominally obese men, as OSA is associated with increased cardiovascular morbidity.[1]

CONCLUSIONS

GH treatment increased the severity of OSA in men with abdominal obesity without any effect on subjective daytime sleepiness. The possible mechanism appears to be reflected by the GH-induced increase of measures of neck volume. The present results, at least to some extent, argue against that low GH/IGF-I activity is a primary cause of OSA in abdominally obese men.

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