Influence of Disease Control with Pegvisomant on Sleep Apnoea and Tongue Volume in Patients with Active Acromegaly

Berg C¹, Wessendorf TE², Mortsch F¹, Forsting M³, Teschler H², Weischer T¹, Mann K¹, Saller B¹, Herrmann BL¹,5

¹Dept. of Endocrinology and Division of Laboratory Research, University of Duisburg-Essen, Germany
²Dept. of Respiratory and Sleep Medicine, Ruhrlandklinik, University of Duisburg-Essen, Germany
³Dept. of Radiology, University of Duisburg-Essen, Germany
⁴Dept. of Oral and Maxillofacial Surgery, University of Duisburg-Essen, Germany
⁵Div. of Endocrinology and Diabetology, Technology Center Bochum, Germany

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Address for correspondence:
Christian Berg, M.D.
Department of Endocrinology and Divison of Laboratory Research
University of Duisburg-Essen
Hufelandstr. 55
D - 45 122 Essen, Germany
Phone: ++49 - 201 - 723 - 84211
Fax: ++49 - 201 - 723 - 5799
e-mail: christian.berg@uni-essen.de
Abstract

Objectives: Sleep apnoea has been consistently reported to occur in acromegaly. In uncontrolled patients, the severity of sleep apnoea influences physical activity in the daytime. We investigated the influence of disease activity on tongue volume and sleep apnoea treated with the GH-receptor antagonist pegvisomant in poorly controlled patients with acromegaly under octreotide.

Design and methods: 12 patients with active acromegaly (6 females; 6 males; mean age 57±15 y; BMI 29.4±4.2 kg/m²; mean±SD) were treated with pegvisomant (13.5±5.0 mg/die) for 6 months. Tongue volume was examined by magnet resonance imaging and sleep apnoea was characterized by polysomnography before and after 6 months treatment with pegvisomant. The mandibular length was determined by lateral x-ray films.

Results: IGF-1 levels decreased after 6 months in all patients (407±114 to 199±23 µg/L; p=0.0001). The tongue volume decreased (105±33 to 83±33 ml; p=0.007) as well as the apnoea-hypnoea-index (AHI) (23±22 to 18±18 /h; p=0.0066). The mandibular length correlated with the initial tongue volume (r²=0.6072, p=0.0028).

Conclusion: In conclusion, successful treatment with pegvisomant can decrease tongue volume, which has benefits for coexisting sleep disordered breathing.
Introduction

Patients with acromegaly have an increased risk of cardiovascular diseases (1-5), cancer (6, 7), and thyroid diseases (8, 9). Sleep apnoea has been consistently reported to occur in acromegaly (10-12). Obstructive sleep apnoea has been attributed to soft-tissue hypertrophy of the upper airway which may predispose to obstruction during sleep either directly by tissue bulk or alteration of pharyngeal collapsibility (13, 14). The relationship between disease activity of acromegaly and sleep apnoea has been controversial with some authors showing a positive correlation between levels of GH and sleep apnoea indices (13, 16) while others did not (10, 17).

The growth hormone antagonist Pegvisomant has been shown to reduce IGF-levels and lead to an amelioration of clinical features of acromegaly such as reduction of soft-tissue swelling. Images of magnet resonance imaging are able to calculate the tongue volume and to determine the effect of treatment for acromegaly as described in a previous study by Herrmann et al. with octreotide in patients with acromegaly (38). To address this issue, we have performed a prospective study to characterize the sleep apnoea of patients with acromegaly and the effect of a 6-months treatment with Pegvisomant.

Patients and methods

Patients

Twelve patients (6 females, 6 males) with a mean age 57±15 years (range 31-77) with uncontrolled active acromegaly under medical treatment with octreotide were included in the study. They were recruited from the Department of Endocrinology, University of Duisburg-Essen in Germany over a 36-months period between 2005 and 2008. The diagnosis of acromegaly was made on the basis of physical examination, IGF-1 and GH levels after an oral glucose load (75 g) (20). 4 patients had microadenomas, 8 patients had macroadenomas. All had undergone surgery for pituitary adenoma (7±5 years before starting pegvisomant) and
none had defects of visual field assessments. Six patients had TSH-deficiency, five patients had ACTH-deficiency and five patients were LH/FSH deficient. All patients were pre-treated with octreotide acetate (Sandostatin LAR®, Novartis Pharma GmbH, Basel, Switzerland). Due to elevated IGF-I levels pegvisomant treatment was started at a dose for 10 mg daily.

Sleep studies (polysomnography) and tongue volume (MRI) were performed at baseline and after 6 months of treatment. The mean BMI was 28.9±3.9 kg/m² (range 23.2-36.7). Eight patients had arterial hypertension and were treated sufficiently with antihypertensive drugs. At baseline, the mean blood pressure was 134±3 / 85±3 mmHg.

**Hormone assays**

Serum IGF-I concentrations were measured by an Immulite assay, Siemens Medical Solutions, Germany. Intra- and interassay CVs for low IGF-I concentrations were 2.4% and 5.2%, respectively.

**Measurement of tongue volume**

All examinations were performed in supine position on a 1.5 T MR-scanner (Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany) equipped with a high-performance gradient system characterized by an amplitude of 40 mT/m and a slew rate 200 mT/m/ms. A head/neck phased-array surface coil was used for signal reception. Tongue volumes were measured by employing a 2 D True-Fisp sequence in sagittal slice orientation without distance factor. A head phased-array surface coil was used for signal reception. In order to avoid motion artefacts the volunteers were asked not to move their tongue during the examination. Furthermore, all patients also underwent a 3D FLASH MR-examination to evaluate the pharyngeal space and underwent a chewing and swallowing examination using a real-time TrueFISP with an oral contrast bolus. Similar examinations were performed in previous
A head and neck phased-array surface coil was used for signal reception. For oral contrast administration 0.5 ml gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) was mixed with 100 ml of normal commercially available vanilla pudding (concentration 1:200). After that a small piece of banana was mixed into this solution in order to increase the volume and viscosity of the contrast solution. Prior to the examination all patients were asked to test-chew and swallow a small bolus in supine position outside of the magnet. There were no signs of aspiration in any of the patients with acromegaly. For the examinations a plastic spoon was used to administer the contrast-agent bolus while the subjects were in supine position and placed in the head coil.

All images were transferred onto a workstation (Virtuosos, Siemens Medical Systems, Erlangen, Germany) and reviewed by a board certified radiologist.

Polysomnography

Complete overnight polysomnography (PSG) using the Compumedics System (Melbourne, Australia) was performed between 10 p.m. and 7 a.m. Two-channel electroencephalography, electrooculography, and chin electromyography were performed using standard methods. Oronasal airflow was recorded by thermistor; thoracic and abdominal respiratory efforts were measured by impedance plethysmography. Oxygen saturation was measured by finger pulse oximetry (ResMed Model 305A, San Diego, California, USA), and electrocardiography was performed from a precordial lead. Body position was monitored by a position sensor. During PSG patients were observed by infrared video surveillance. Patients had been instructed to behave during the night as “normally” as possible. Sleep data were staged manually according to standard criteria (24), and the arousals were scored according to the criteria of the American Sleep Disorders Association (25).

Apnoea was defined as cessation of airflow or reduction in thermistor signal to less than 10% of the normal flow and lasting for at least 10 s. Apnoeas less than 10 s were counted if they
were followed by either an arousal or an oxygen desaturation of 4% or more. Events were classified as obstructive (clear obstructive or mixed with a clear obstructive component in the event) or central events according to the respiratory effort channels. Hypopnea was defined as a discernible reduction in airflow of at least 10 s duration followed either by arousal or a desaturation of 4% or more.

The respiratory events were scored in accordance to the American Academy of Sleep Medicine Task Force recommendations (25). The apnoea-hypopnea index (AHI) was calculated as the number of all respiratory events per hour of sleep. An AHI shorter than 5 was defined as normal. Sleep related breathing events were considered mild when AHI was between 5 and 15 events per hour, moderate in cases of AHI between 15 and 30 events per hour and severe if AHI was greater than 30 events per hour. Clear oxygen saturation (SaO₂) artifacts were excluded manually. Oxygen indices were than calculated by the software from the SaO₂ curve with minimal SaO₂ being the lowest saturation reached during sleep and with average minimal SaO₂ being the mean of all saturation values reached during all respiratory events.

X-Ray-Examinations

Lateral x-ray scans were made under standard conditions, in centric occlusion with control of head position, to determine the length of the mandible (distance tgo h – Gn, figure 2). The patients had their radiographs taken at a constant distance of 1.5 m between the x-ray source and the median plane of the head.

Statistical analyses

The data, if not marked otherwise, represent the mean ± standard deviation. Absolute differences between time points (e.g. tongue volume at baseline and after the observation period) were analyzed per group using the paired Wilcoxon signed rank test. All tests were done two-tailed, p-values <0.05 were considered statistically significant. Correlations between
mandibular length and tongue volume were measured by linear regression (p-values <0.05 were considered statistically significant). Statistical analyses were performed using GraphPad InStat version 3.02 (GraphPad Software, San Diego, California USA).

Results

Four patients received 10 mg, two patients 15 mg, five patients 20mg and one patient 30 mg Pegvisomant (Somavert®) every day s.c.. Overall, IGF-1 levels decreased significantly from 408±114 to 199±80 µg/L (p<0.001) (s. figure 3). After treatment with Pegvisomant, the age-adjusted IGF-1 levels were normalized in all patients. At baseline, 8/12 patients (66%) had moderate or severe obstructive sleep apnoea with a mean apnoea-hypnoea-index (AHI) of >15/h (range 1-80.2) and no patient had central sleep apnoea.

Effects of treatment on tongue volume

Tongue volume decreased significantly (figure 4; 105±33 at baseline vs. 83±20 ml, after 6 months, p=0.007). The IGF-1 levels at baseline and after treatment correlated significantly with BMI-adjusted tongue volume (figure 5; r=0.40, p=0.05). Moreover, the disease duration correlated with the BMI-adjusted tongue volume (r=0.71, p=0.006). Mean length of the mandible was 9.0±1.0 cm and correlated significantly with BMI-adjusted tongue volume (figure 6, r=0.78, p=0.003)

Effects of treatment on sleep-disordered breathing

After 6 months of pegvisomant treatment, there was a significant decrease of AHI of 24±28 % (23.4±21.5/h vs. 17.5±17.8/h, p=0.007). At baseline, three patients had an AHI >30/h, five had an AHI of 15-30/h, two an AHI of 5-14/h and two an AHI <5/h. After treatment, one
patient had an AHI >30/h, six patients an AHI of 15-30/h, three an AHI of 5-14/h and two an AHI <5/h. AHI decreased in 9/12 (75%) of the patients (figure 7).

Although a decrease in mean levels of IGF-1 and an improvement in mean AHI were seen in the study group, no correlation was noted between the absolute decrease of IGF-1 levels and the changes in AHI. AHI did not correlate with BMI (p=0.24), BMI-adjusted tongue volume (p=0.52) nor age (p=0.24) but with length of the mandible (r=0.62, p=0.03). Minimum oxygen saturation did not change significantly (83±3% at baseline vs. 85±4% after 6 months).

**Discussion**

In the present study, we found a prevalence of sleep apnoea syndrome of 83% in patients with active acromegaly, confirming reports from previous studies (33,34,37,38). Successful treatment via IGF-I normalization led to a 24% improvement of the AHI. We have shown that soft-tissue swelling determined by tongue size volume by magnet resonance imaging can effectively be reduced by treatment with pegvisomant.

Sleep apnoea is a common complication in uncontrolled acromegaly and is an established additional cardiovascular risk factor potentially increasing morbidity and mortality observed in acromegaly (10, 15-17). Treatment of obstructive sleep apnoea with nasal continuous airway pressure therapy may result in a significant reduction of cardiovascular complications like hypertension (25, 26, 27).

We confirmed previous studies that suggested obstructive rather than central sleep apnoea being the prevalent form of sleep disordered breathing in acromegaly as none of our patients had central but all had obstructive sleep apnoea (28,39).
Regarding predisposing factors, previous studies identified anatomical abnormalities in acromegaly by using lateral x-ray films with cephalometric landmarks and reference lines like dorsocaudal rotation of the mandible, increase in facial height and narrowing of the depth of the bony framework of the nasopharynx (27, 29-31).

Furthermore soft-tissue swelling is a relevant factor in patients with acromegaly for the obstruction of the upper airway (26-28). Studies suggested that upper airway narrowing caused by enlarged uvula and narrowed pharyngeal airway may play a more relevant role in the development of obstructive sleep apnoea in acromegalic patients than skeletal anomalies (27, 29-31, 40). Beside a large uvula, it is pronounced macroglossia narrowing pharyngeal airway space in acromegalics. This was demonstrated in a previous study by Herrmann et al. (38) where active acromegalic patients had significantly increased tongue volumes by MRI in comparison to an age-matched healthy control group. MRI, compared to radiographs, has the advantage of more precise delineation of soft-tissue and determination of tongue volume. We have adjusted the tongue volume to the BMI, because height and weight are positively related to the tongue volume. Like in the study by Herrmann et al. we were able to demonstrate that IGF-1 levels were closely correlated to the BMI-adjusted tongue volume (38).

This is the first study evaluating the effect of the GH-receptor antagonist pegvisomant on soft-tissue swelling of the tongue. There is evidence that IGF-I normalization leads to reduction of soft-tissue swelling and is beneficial on acromegalic organ hypertrophy which has e.g. already been shown by Colao et al. by the analysis of cardiac size in a similar cohort of acromegalic patients treated for the same time (32). Pegvisomant treatment has been reported to normalise IGF1 levels in more than 90% of acromegalic patients (41). Pegvisomant is a GH-receptor antagonist that blocks GH activity by inhibiting functional dimerisation of the GH-receptor. Hence it is blocking its biological activity and inhibiting IGF1 production (42). In our study
we observed reduction of soft-tissue swelling by a 22% reduction of tongue volume after 6 months.

Regarding sleep apnoea, the correlation between disease activity and severity of apnoea is controversial and it is unclear whether and to what extend sleep apnoea subsides after biochemical remission of the disease. So far, this is the only study evaluating the effect of pegvisomant on sleep disordered breathing. Until now previous studies have only evaluated the effect of surgery or medical therapy with somatostatin analogues on the reversibility of sleep apnoea after IGF-I normalization with conflicting results. Rosenow et al. (13) found a relative high frequency of sleep apnoea in patients with treated acromegaly, at least of 21%, with a positive correlation with GH/IGF1 levels, age as well as neck and index-finger circumference as measures of soft tissue hypertrophy. Some studies showed significant improvement or cure after adenomectomy (18, 46), while others found persisting nocturnal breathing abnormalities (47) in patients previously treated with pituitary surgery (34) or only slight to moderate improvement despite normalized or decreased hormonal levels (48) probably due to the irreversible changes of the craniofacial region and upper respiratory tract (14, 27, 30). Finally, there are many reports of relief during treatment with s.c. or long acting release octreotide (28,38,49), although the sleep apnoea can persist after GH/IGF-I normalization (38, 49).

Although, we have seen a significant overall decrease of AHI of 24% after treatment with pegvisomant, this is far from cure, in particular in patients with severe obstructive sleep apnoea (AHI >30/h) probably due to the irreversible changes of the upper respiratory tract. Beside obesity, hypertension and hormonal alterations, it could recently been shown that craniofacial abnormalities have a relevant and irreversible influence on sleep apnoea-related nocturnal hypoxemia (44, 45). In fact, we have found that tongue volume and apneic episodes
were affected by the increased length of the mandible in acromegalics. These are irreversible craniofacial changes that together with soft tissue swelling and enlargement of the tongue and uvula are suggested to have major impact on the obstructive sleep disorders and its complications (27, 38).

Moreover, it has been shown that independent factors like age may influence sleep disorders in patients with acromegaly. Considering the fact, that body fat is increased in patients with acromegaly after cure or successful treatment (35, 36), long term observation of sleep apnoea in acromegalic is recommended. In our study AHI did not correlate with age or BMI, possibly due to the small number of patients studied. However some studies have described the BMI-independent effect of age, showing an approximate doubling of AHI every ten years, probably due to age-related weakening of the upper airway musculature (25).

Although we were able to demonstrate a correlation between the biochemical activity in acromegaly and soft-tissue swelling of the tongue, we did not find any correlation between apneic episodes and soft-tissue swelling of the tongue. This may be due to multifactorial pathogenesis of sleep apnoea syndrome and to the small number of patients. It could be supposed that periods of disease remission longer than what we observed could be necessary.

In summary, we have shown that treatment with pegvisomant significantly reduces tongue volume and the severity of sleep apnoea. The high prevalence of obstructive sleep apnoea in patients with active acromegaly demonstrates that screening for sleep apnoea should be mandatory in the diagnostic work-up of acromegalic patients. Regarding treatment of acromegaly, these findings strengthen the need not only for an early diagnosis of sleep apnoea but for aggressive treatment of the disease.
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Declaration of Interest statement

CB received German Pfizer grant of the German Endocrine Society for 2004/05 for another project and has received lecture fees from Pfizer Germany, Novartis Germany and NovoNordisk Germany in the past.


Legends

Figure 1: Measurement of the tongue volume by employing a 2 D True-Fisp sequence in sagittal slice orientation with magnet resonance imaging in one patient with acromegaly at baseline (a) and after a 6-months treatment period of pegvisomant (b).

Figure 2: Lateral x-ray film of a patient with acromegaly and landmarks of standardized lateral cephalometric analysis (A: maxillar apical point; B: mandibular apical point; Gn: gnathion; Pg: pogonion; S: sella; N: nasion; Sp: spina nasalis anterior).

Figure 3: Changes of IGF-I levels of 12 patients with acromegaly before and after treatment with pegvisomant over a 6-months period.

Figure 4: Tongue volume of patients with acromegaly at baseline and after a 6-months treatment period of pegvisomant with normal age-adjusted IGF-1 levels (n=12).

Figure 5: Correlation between IGF-1 levels and BMI-adjusted tongue volume in 12 patients with active acromegaly before treatment with pegvisomant over a 6-months period and after treatment.

Figure 6: Correlation between mandibular length and BMI-adjusted tongue volume in 12 patients with acromegaly before and after treatment with pegvisomant over a 6-months period.

Figure 7: Changes of AHI (apnoea-hypnoea index) of 12 patients with acromegaly before and after treatment with pegvisomant over a 6-months period.
Figure 1

a)  b)
Figure 2
Figure 3

[Graph showing the decrease in IGF-I levels from baseline (0) to 6 months. The x-axis represents time in months, ranging from 0 to 6. The y-axis represents IGF-I levels in ng/ml, ranging from 0 to 750. Several lines represent individual subjects, all showing a downward trend from left to right.]
Figure 4

![Box plot showing tongue volume comparison between baseline and 6 months.](image_url)

- **Tongue Volume [ml]**
- **Baseline** vs **6 months**
- **p-value**: 0.0068
Figure 5:

A scatter plot shows the relationship between tongue volume/BMI and IGF-I [ng/ml]. The correlation coefficient is $r=0.40$ and the p-value is $p=0.05$. The data points are dispersed along the trend line, indicating a positive correlation.
Figure 6:

$r^2=0.60$

$p=0.0028$
Figure 7: