Effects of Octreotide on Sleep Apnoea and Tongue Volume (MRI) in Patients with Acromegaly

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Abstract

Objectives: Sleep apnoea has been consistently reported to occur in acromegaly. Both obstructive apnoeas, in which apnoeas are due to intermittent obstruction of the upper airways, as well as central apnoeas are known to occur. Because the relationship between disease activity and severity of sleep apnoea is currently unclear, we have performed a prospective study to address this issue.

Design and methods: In 14 newly diagnosed patients with active acromegaly (8 females; 6 males; mean age 57±4 yr; IGF-1 583±48 µg/L; GH 13.5±7.0 µg/L (mean±SEM)), tongue volume and signal intensity of the tongue were examined by magnet resonance imaging and sleep apnoea was characterized by polysomnography before and after 6 months treatment with octreotide acetate (Sandostatin LAR 10-30 mg every 4 weeks i.m.).

Results: The initial tongue volume was significantly higher in patients with acromegaly (151±9 ml; females 133±10 ml; males 172±10 ml) in comparison to the BMI and age-matched healthy control group (97±5 ml, $p<0.001$; females 75±1 ml, $p<0.001$; males 120±3 ml, $p<0.003$). After treatment with octreotide, IGF-1 was normalized within the age-adjusted normal range in 50% of the patients. In these patients tongue volume significantly decreased (120±14 ml, $p<0.05$) in comparison to the persistant uncontrolled group of acromegalics (137±10 ml, p=n.s). Overall, tongue volume (128±8 ml, $p<0.05$) and the signal intensity ratio of the tongue decreased significantly after treatment with octreotide acetate (120±3 vs. 105±3, $p=0.003$). The BMI-adjusted tongue volume correlated with IGF-1 levels ($r=0.60$; $p<0.002$) and the disease duration ($r=0.71$; $p=0.006$).

At baseline, 50% had obstructive sleep apnoea with a mean respiratory disturbance index (RDI) of >20/h (range 5.1-91.5) and no patient had central sleep apnoea. After 6 months octreotide treatment, there was a 28±10% decrease of RDI. However, RDI did not correlate with IGF-1 nor GH levels, but correlated positively with BMI ($r=0.58$, $p=0.001$) and age ($r=0.46$, $p=0.02$). *Conclusions:* Obstructive sleep apnoea, but not central sleep apnoea frequently occurs in patients with active acromegaly. Successful treatment with octreotide can decrease tongue volume, which may have benefits for coexisting sleep disordered breathing.

Introduction

Patients with acromegaly predominantly have an increased risk of cardiovascular diseases (1-5), cancer (6, 7), and thyroid diseases (8, 9). Sleep apnoea, the phenomenon of recurrent cessation of airflow during sleep, has been consistently reported to occur in acromegaly (10-12). The mechanisms by which apnoeas occur in acromegaly have not been clearly delineated. 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). Central sleep apnoea has been attributed to both partial obstruction leading to destabilization of ventilatory control and to a defect of ventilatory control due to hormonal influence (15). 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 somatostatin analogue octreotide has been shown to reduce GH secretion by pituitary adenomas, and lead to a amelioration of clinical features of acromegaly such as reduction of soft-tissue swelling (18, 19). Images of magnet resonance imaging are able to calculate the tongue volume and to determine the effect of treatment with octreotide in patients with acromegaly. 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 octreotide acetate.

Patients and methods

Patients

Fourteen patients (8 females, 6 males) with a mean age 57±4 years (range 29-73) with untreated active acromegaly were included in the study. They were recruited from the Clinic of Endocrinology, University of Essen in Germany over a 12-months period between 2002 and 2003. 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). 8 patients had microadenomas, 6 patients had macroadenomas. None of them had defects of visual field assessments. Four patients had TSH-deficiency, one patient ACTH-deficiency and one patient was LH/FSH deficient. Octreotide acetate (Sandostatin LAR®, Novartis Pharma GmbH, Basel, Switzerland) was started at a dose for 20 mg every 4 weeks. After the third injection, the dose was reduced to 10 mg every 4 weeks in those subjects with a mean of 2-h GH profile (assessed by sampling every 30 min) <1 µg/L and IGF-1 levels within the normal range for age. In those with a mean of 2-h GH profile >2.5 µg/L or IGF-1 levels above normal range for age, the dose was increased to 30 mg. Mean 2-h GH levels and IGF-1 (mean of two fasting samples taken at a 1 h interval) were assessed at baseline and week 12 and 24. Sleep studies (polysomnography) and tongue volume (MRI) were performed at baseline and after 6 months of treatment. The mean BMI was 30.8±1.5 kg/m² (range 26.1-43.4). Ten patients had arterial hypertension and were treated sufficiently with antihypertensive drugs. At baseline, the mean blood pressure was 129±4 / 74±2 mmHg.

Control group

A group of 50 volunteers, comparable for age (51±2 years, range 28-79), BMI (25.2±1.2 kg/m²) and sex distribution (25 females, 25 males) served as non-acromegalic controls for the tongue volume (MRI). None of them had symptoms or signs of sleep apnoea syndrome.

Hormone assays

Serum GH levels were determined by a chemiluminescence immunometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st international standard (80/505) for human GH. Normal range was ≤5 μg/l. Intra- and interassay coefficients of variation (CVs) for a low point of the standard curve were 5.4% and 7.9%, respectively. Plasma IGF-I concentrations were measured by an immunoradiometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st International Reference Reagent 87/518. Intra- and interassay CVs for low IGF-I concentrations were 2.4% and 5.2%, respectively. Normal range of IGF-1 levels: 182-780 μg/L (16-24 years), 114-492 μg/L (25-39 years), 90-360 μg/L (40-54 years) und 71-290 μg/L (>54 years).

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 (figure 1). 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 studies (21-23). 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. For quantitative analysis, regions of interest (ROI) were placed in the lumen of the tongue. Image noise, defined as the standard deviation of signal intensities measured in an ROI placed outside the body was determined. Based on these measurements Signal-to-Noise Ratios (SNR) for representative parts were calculated: SNR = (SI (tongue) / SI (SD) noise).

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 shorter 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. Hyponea 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 disturbance index (RDI) was calculated as the number of all respiratory events per hour sleep. A RDI <5 was defined as normal, a RDI of 5-20 as borderline, and a RDI of >20 as definitely pathological. Clear oxygen saturation (SaO_2) artifacts were excluded manually. Oxygen indices were than calculated by the software from the SaO_2 curve with minimal SaO_2 being the lowest saturation reached during sleep and with average minimal SaO_2 being the mean of all saturation values reached during all respiratory events.

Statistical analyses

The data, if not marked otherwise, represent the mean ± standard error. Differences between two groups were tested by Mann-Whitney U-test as a nonparametric procedure. 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.

Results

Effects of treatment on tongue volume

The initial tongue volume was significantly higher (36%) in patients with acromegaly (151±9 ml) in comparison to the BMI and age-matched healthy control group (97±5 ml, p<0.001). Females had a lower tongue volume than males. Females with active acromegaly (133±10 ml) had a significant higher tongue volume than females of the control group (75±1 ml; p<0.001). Males with active acromegaly (172±10 ml) had a significant higher tongue volume than males of the control group (120±3 ml; p<0.003).

Seven patients received 20 mg, six patients 30 mg and one patient 10 mg octreotide acetate (Sandostatin LAR®) every 28 days i.m. Overall, IGF-1 levels significantly decreased from 583±40 to 363±57 µg/L (p<0.001), GH decreased from 13.4±7.0 µg/L (range 2.1-103.0) to 4.6±3.9 µg/L (range 0.6-40.5) (p<0.001). After treatment with octreotide acetate, the age-adjusted IGF-1 levels were normalized in 50% of patients. In these patients tongue volume significantly decreased (figure 2; 120±14 ml, p<0.05) in comparison to the persistant uncontrolled group of acromegalics (137±10 ml, p=n.s). Overall, tongue volume decreased significantly after treatment with octreotide acetate (128±8 ml, p<0.05). We have adjusted the tongue volume to the BMI, because height and weight are positively related to the tongue volume. The IGF-1 levels at baseline and after treatment correlated significantly with BMI-adjusted tongue volume (figure 3; r=0.60, p=0.002), whereas GH levels did not. Moreover, the disease duration correlated with the BMI-adjusted tongue volume (figure 3; r=0.71, p=0.006).

The signal intensity correlates positively with water/oedema and offers an exact quantitative analysis of the treatment effect on soft-tissue swelling. After treatment with octreotide, the signal intensity ratio of the tongue significantly decreased (120±3 vs. 105±3, p=0.003). The signal intensity ratio of the tongue correlated significantly with IGF-1 levels (figure 3; r=0.46, p=0.02).

Effects of treatment on sleep-disordered breathing

At baseline, 50% of patients had obstructive sleep apnoea with a mean respiratory disturbance index (RDI) of >20/h (range 5.1-91.5) and no patient had central sleep apnoea. After 6 months octreotide treatment, there was a 28±10% decrease of RDI. At baseline, 50% had a RDI >20/h, 29% a RDI 11-20/h, 21% a RDI 5-10/h and none a RDI <5/h. After treatment, 46% had a RDI >20/h, 8% a RDI 11-20/h, 38% a RDI 5-10/h and 8% a RDI <5/h (table 1). RDI decreased in 64% (9/14) of the patients (figure 4).

Although a decrease in mean levels of IGF-1 and GH and an improvement in mean RDI were seen in the study group, no correlation was noted between the absolute decrease of IGF-1 or GH levels and the changes in RDI. But RDI correlated positively with the BMI (r=0.58, p=0.001) and age (r=0.46, p=0.02). Minimum oxygen saturation did not change significantly (81±3% at baseline vs. 83±2% after 6 months).

Discussion

In the present study, we have demonstrated that magnet resonance imaging can sufficiently determine tongue size and that treatment with octreotide can effectively reduce tongue volume in patients with newly diagnosed acromegaly. 50% had obstructive sleep apnoea with a mean respiratory disturbance index (RDI) of >20/h. After treatment, we have seen a 28% decrease of the number of apneic events.

Beside cardiovascular diseases and cancer, sleep apnoea is a further complication of GH-excess in untreated acromegaly (10, 15-17). Considering the association of sleep-disordered breathing with cardio- and cerebrovascular disease (23, 24), it becomes obvious that the increased mortality of patients with acromegaly may not only be due to cardiovascular diseases and cancer but also due to sleep apnoea. Moreover, it is now well established, that hypertension and cardiovascular diseases are associated with sleep apnoea. The prevalence of hypertension in obstructive sleep apnoea is up to 3 times higher than in the normal generation (25, 26). Treatment of obstructive sleep apnoea with nasal continuous airway pressure therapy may result in a significant decrease of elevated blood pressure in hypertensive patients (27).

Sleep-disordered breathing can be classified as obstructive or central sleep apnoea. Grunstein et al. reported that patients with a central form of sleep apnoea have significantly higher GH and IGF-1 levels than patients with obstructive disease (10). Albeit the authors speculated that increased brain somatostatin (a potential consequence of high circulating GH) might be responsible for the generation of central apneic episodes, the success of octreotide in relieving central sleep apnoea argues against the proposed primary role of somatostatin as a causative agent (15). None of our patients with active acromegaly had predominantly central sleep apnea neither before nor after treatment, indicating that a larger number of acromegalic patients have to be studied to clarify this issue.

Consistently to previous studies, we have seen that 50% of our patients with active acromegaly had moderate to severe obstructive sleep apnoea (10, 15). The soft-tissue swelling of the tongue might be responsible for the upper airway obstruction (26-28). Previous studies tried to characterize anatomical differences of acromegalic patients in comparison to healthy non-acromegalics by using lateral x-ray films with cephalometric landmarks and reference lines. From those studies (27, 29-31), there are anatomical skeletal abnormalities predisposing to obstructive sleep apnoea: maxillary and mandibular retrognathism, dorsocaudal rotation of the mandible, enlargement of the anterior and posterior facial height, and narrowing of the depth of the bony framework of the nasopharynx. Moreover, patients with acromegaly have a larger uvula and a narrowed pharyngeal airway space caused by changes in pharyngeal soft-tissues swelling than the healthy population (27, 29-31).

Beside a large uvula, macroglossia narrows pharyngeal airway space. Magnet resonance imaging, compared to radiographs, has the advantage of more precise delineation of soft-tissue and determination of tongue volume. The present study has shown, that magnet resonance imaging of the pharynx revealed a significant higher (plus 36%) tongue volume in patients with active acromegaly in comparison to an age-matched healthy control group. We have adjusted the tongue volume to the BMI, because height and weight are positively related to the tongue volume. IGF-1 levels correlated closely to the BMI-adjusted tongue volume. The evidence that only a decrease of IGF-I could be beneficial on organ hypertrophy has already shown by analysis of cardiac size in a similar cohort treated for the same time (32). As it has been shown in several studies about complications in patients with acromegaly (1, 33), the disease duration correlated with the BMI-adjusted tongue volume.

Octreotide acetate, a long-acting somatostatin analogue which effectively reduces GH secretion in acromegaly, has been shown to decrease soft-tissue swelling in acromegaly (18, 19). After treatment with octreotide acetate, tongue volume significantly decreased, despite of the IGF-1 normalization in only 50% of the patients after 6 months.

Although, we have seen overall a 28% decrease of RDI after treatment with octreotide, RDI did not normalized in patients with severe obstructive sleep apnoea (RDI >20/h). The mechanisms leading to improvement have not elucidated, since sleep apnoea may persist despite normalization of GH levels or may improve markedly with only partial biochemical remission (17, 34). Similar to our observations, Grunstein did not find any association between hormonal activity and the presence of sleep apnoea, in contrast to a previous study of Hart and collegues (16), who reported that only patients with active acromegaly had sleep apnoea. Despite the lack of definitive documentation, it is generally accepted that improvement of sleep apnoea is mediated through a decrease in upper airway obstruction secondary to several factors, including reduction of upper airway soft-tissue bulk or collapsibility and improvement of upper airway muscle function. Moreover, RDI correlated positively with the BMI and age, indicating that independent factors of the disease activity may influence sleep disorders in patients with acromegaly. Considering the fact, that body fat increased in patients with acromegaly after cure or successful treatment (35, 36), long term observation of sleep apnoea in acromegalic is recommended.

Although we were able to demonstrate a correlation between the improvement in biochemical activity via IGF-1 and soft-tissue swelling of the tongue, we did not find any correlation between apneic episodes and tongue volume or disease activity. This may be due to the small number of patients and the multifactorial pathogenesis of sleep apnoea syndrome.

In summary, our findings have shown that magnet resonance imaging revealed a higher tongue size in patients with acromegaly and that treatment with octreotide significantly reduces tongue volume. The presence of 50% of severe obstructive sleep apnoea in patients with active acromegaly clarifies, that screening for sleep apnoea should be included in the diagnostic work-up of acromegalic patients.

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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 octreotide (b)

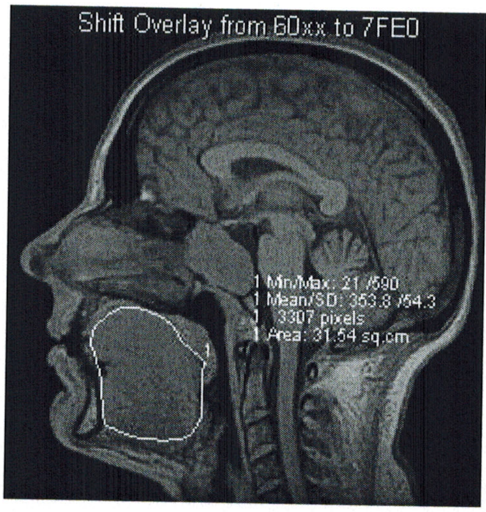
Figure 2: Tongue volume of controls □, of patients with acromegaly at baseline ■, and after a 6-months treatment period of octreotide with normal age-adjusted IGF-1 levels (n=7) ▨ and persistent elevated IGF-1 levels (n=7) ▦

Figure 3: Correlation between IGF-1 levels and BMI-adjusted tongue volume (a), signal intensities of the tongue (b) and correlation between disease duration and BMI-adjusted tongue volume (c) in 14 patients with newly diagnosed acromegaly before and after treatment with octreotide acetate over a 6-months period

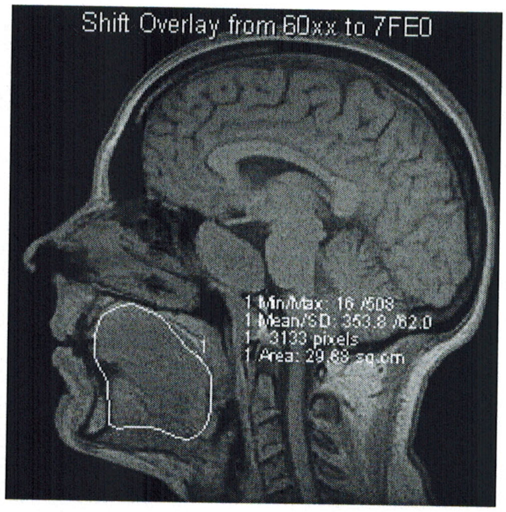
Table 1: Distribution of RDI (respiratory disturbance index) of 14 patients with newly diagnosed acromegaly before and after treatment with octreotide acetate over a 6-months period

Figure 4: Changes of RDI (respiratory disturbance index) of 14 patients with newly diagnosed acromegaly before and after treatment with octreotide acetate over a 6-months period

Figure 1


Shift Overlay from 60xx to 7FE0
1 Min/Max: 21 /590
1 Mean/SD: 353.8 /54.3
1 3307 pixels
1 Area: 31.54 sq.cm

a)


Shift Overlay from 60xx to 7FE0
1 Min/Max: 16 /508
1 Mean/SD: 353.8 /62.0
1 3133 pixels
1 Area: 29.83 sq.cm

b)

Figure 2

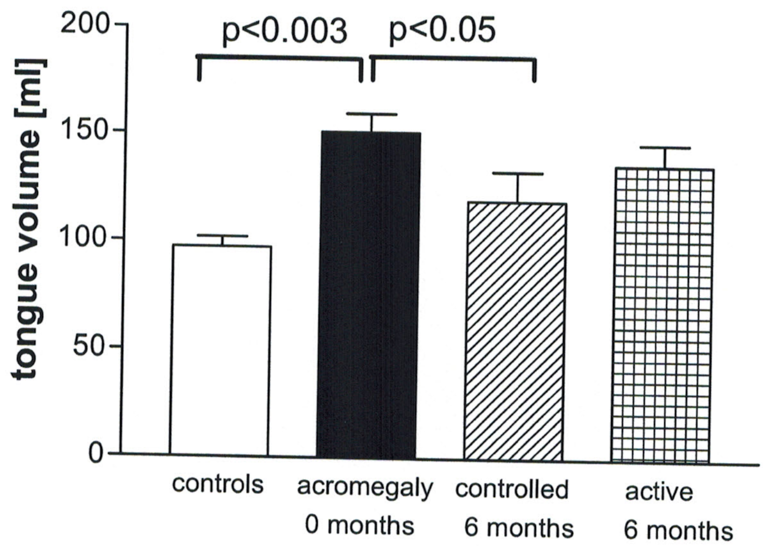
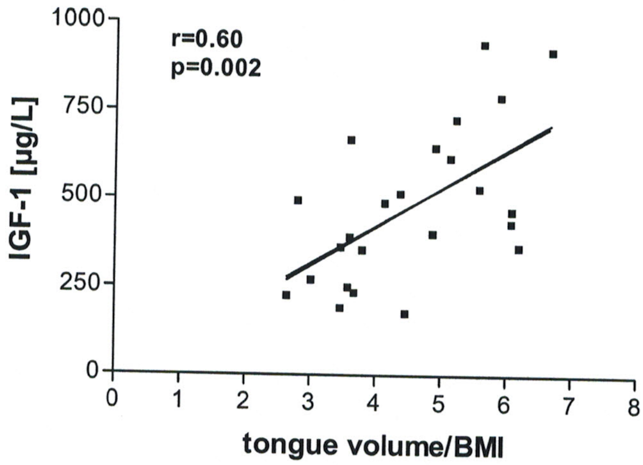


Table 1

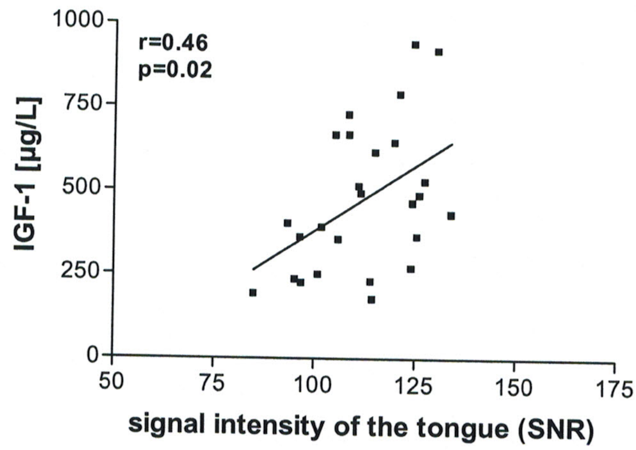
	RDI baseline	RDI after 6 months
>20/h	50%	46%
11-20/h	29%	8%
5-10	21%	38%
<5/h	0%	8%

Figure 3

a)


r=0.60
p=0.002
IGF-1 [µg/L]
1000
750
500
250
0
0
1
2
3
4
5
6
7
8
tongue volume/BMI

b)


r=0.46
p=0.02
IGF-1 [µg/L]
1000
750
500
250
0
50
75
100
125
150
175
signal intensity of the tongue (SNR)

c)

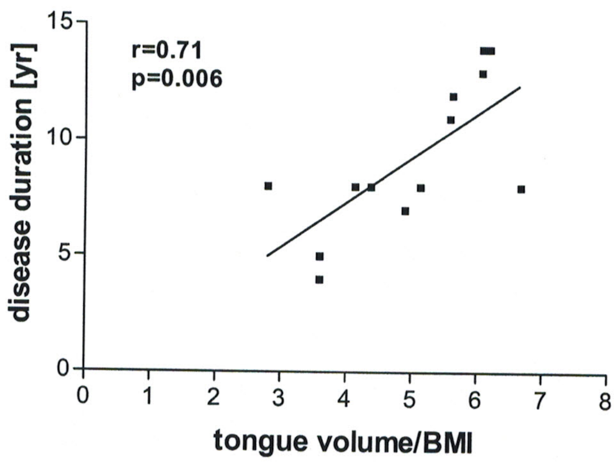
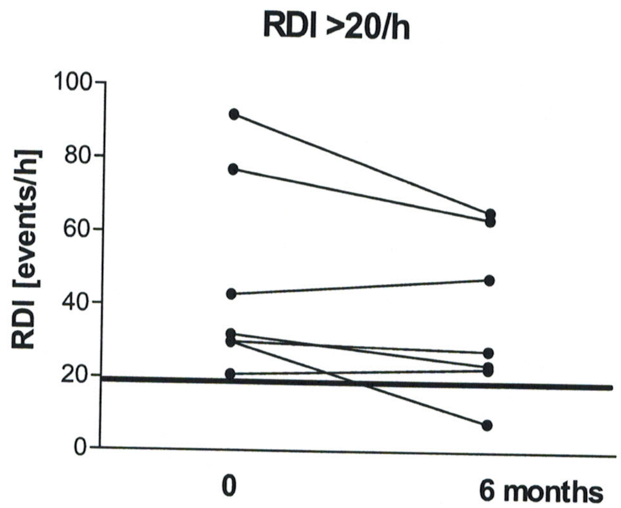
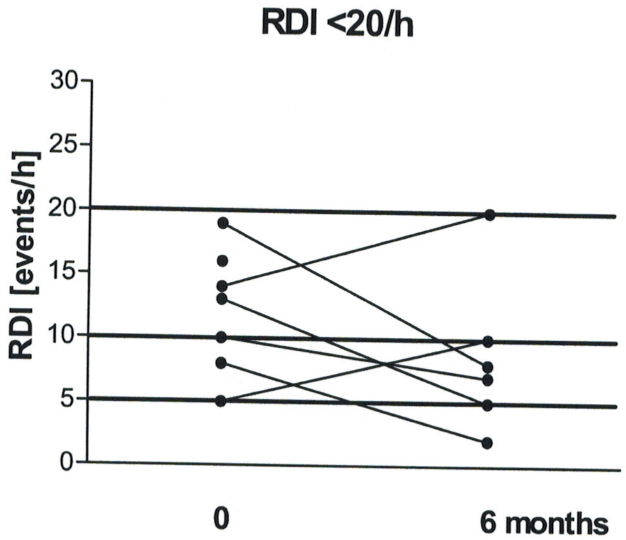

r=0.71
p=0.006
disease duration [yr]
15
10
5
0
0
1
2
3
4
5
6
7
8
tongue volume/BMI

Figure 4


RDI >20/h
RDI [events/h]
100
80
60
40
20
0
0
6 months


RDI <20/h
RDI [events/h]
30
25
20
15
10
5
0
0
6 months