



# Obstructive Sleep Apnea Syndrome in Acromegaly Before and After Treatment

## Tedavi Öncesi ve Sonrası Dönemde Akromegalide Obstruktif Uyku Apne Sendromu

Selda Korkmaz, İlkey Çakır\*, Fahri Bayram\*\*, Züleyha Karaca\*\*, Sevda İsmailoğulları\*\*\*, Murat Aksu\*\*\*

Acıbadem University Faculty of Medicine, Acıbadem Kayseri Hospital, Department of Neurology, Kayseri, Turkey

\*Sivas Numune Hospital, Sivas, Turkey

\*\*Erciyes University Faculty of Medicine, Department of Endocrinology, Kayseri, Turkey

\*\*\*Erciyes University Faculty of Medicine, Department of Neurology, Kayseri, Turkey

### Summary

**Introduction:** Obstructive sleep apnea syndrome (OSAS) prevalence in acromegaly patients is very common compared with general population. It is thought that OSAS in acromegaly patients evolve because of reversible and irreversible anatomical changes. However, reason of anatomical changes has not been known in present. Maybe, Growth Hormone (GH) and insulin-like growth factor 1 (IGF-I) levels could be an important factor in the development of anatomical changes. In this study, we aimed to determine the prevalence of OSAS in acromegaly and to show the correlation between disease activity and OSAS in acromegalic patients.

**Materials and Methods:** Newly diagnosed and treatment naive 15 acromegaly patients were included into the study. Patients were evaluated by polysomnography (PSG) recordings and hormone levels at baseline and 6 months after treatment.

**Results:** Present study showed that OSAS is more common in patients with acromegaly than general population. Moreover, there is no correlation between GH, IGF-I level and apnea-hypopnea index (AHI) both at baseline and 6 months after treatment.

**Discussion:** OSAS is a condition increased morbidity and mortality associated with acromegaly. Early diagnosis and treatment of acromegaly is important in order to prevent progression of anatomical changes leading to OSAS to an irreversible state. If OSAS and its complications had been prevented, morbidity and mortality in acromegaly patients would have been decreased. (JTSM 2014;1:22-7)

**Key Words:** Acromegaly, sleep apnea, GH, IGF-I

### Özet

**Giriş:** Obstruktif uyku apne sendromu (OUAS), akromegalik hastalarda genel popülasyon ile karşılaştırıldığında oldukça sıktır. Akromegalik hastalardaki OUAS'nin bu hasta grubunda gözlenen geri dönüşümlü ya da geri dönüşsüz anatomik değişiklikler ile ilişkili olduğu düşünülmektedir. Bu anatomik değişikliklerin nedeni tam olarak bilinmemekle birlikte, serum Growth hormon (GH) ve insülin benzeri growth faktör-1 (IGF-1) seviyelerinin önemli olduğu düşünülmektedir. Bu çalışmanın amacı, akromegalik hastalardaki OUAS sıklığını belirlemek ve hastalık aktivitesi ile OUAS arasındaki ilişkiyi saptamaktır.

**Gereç ve Yöntem:** Çalışmaya 15 yeni tanı almış ve tedavi başlanmamış akromegali hastası alındı. Hastaların polisomnografi (PSG) kayıtları yapıldı ve bazal hormon değerleri belirlendi. OUAS tanısı alan hastalara sürekli hava yolu basınç (CPAP) tedavisi başlandı. CPAP tedavisi alan hastalarda PSG ve hormonal çalışmalar tekrarlandı.

**Bulgular:** Akromegalik hastalarda OUAS, genel polasyona göre daha sık bulundu. Ancak hem bazal hem de tedavi sonrası yapılan değerlendirmelerde hastalardaki OUAS şiddeti ile hormonal aktivite arasında bir ilişki saptanmadı.

**Sonuç:** OUAS, akromegalik hastalarda mortalite ve morbiditeyi artıran bir durumdur. Akromegali tanısının erken konması, OUAS gelişiminde rol oynayan geri dönüşsüz anatomik değişikliklerin oluşumunu engelleyeceğinden dolayı önemlidir. OUAS varlığı saptandığında uygulanacak CPAP tedavisi akromegalik hastalardaki morbidite ve mortaliteyi azaltıcı etki gösterecektir. (JTSM 2014;1:22-7)

**Anahtar Kelimeler:** Akromegali, uyku apnesi, GH, IGF-I

## Introduction

Acromegaly is a rare, slowly progressive neuroendocrine disorder resulting almost invariably from a growth hormone (GH)-secreting pituitary adenoma. The estimated prevalence and incidence of the disease are respectively 40/1 000 000 and 3-4/1 000 000 in population (1,2). The elevated circulating GH level results in an increased production of other tissue growth factors, such as insulin-like growth factor 1 (IGF-I). IGF-1 and GH levels are used to assess disease activity (2). Increased levels of GH and IGF-1 lead to cardiovascular, metabolic and respiratory complications such as hypertension (HT), diabetes mellitus (DM) and sleep apnea syndrome (SAS) (3-6). Those complications are responsible for mainly increased morbidity and mortality in acromegaly patients (7). Also, presence of SAS in acromegaly patients leads to worsening of systemic conditions such as HT, DM and cardiac arrhythmia (8,9).

SAS is characterized by reduction in quality of sleep and daytime sleepiness due to repetitive apneas or hypopnoeas with arterial oxygen desaturation during sleep. SAS is defined as the presence of at least five episodes of apnea or hypopnea lasting 10 seconds or longer for each hour of nocturnal sleep with daytime somnolence. Clinically, moderate or severe SAS is defined as more than 15 apnea-hypopnea index (AHI). Based on pathophysiological criteria, three types of SAS are defined: The first is central type apnea, characterized by absent or reduced activity of the respiratory center, the second is obstructive type apnea, characterized by intermittent obstruction of the upper airways with preservation of thoracic and abdominal respiratory movements, and the third is mixed type apnea that is a combination of obstructive and central type (10).

Previous studies have described the association between sleep apnea and acromegaly (3,11,12). The prevalence of SAS in acromegaly is thought to be roughly 60%, ranging between 19 and 93% (3,12-14). In most cases, apnea is obstructive type, but one-third of patients have central apnea (3,11,15,16). Although the obstructive type SAS (OSAS) is common in the general population with a prevalence of 2 % in women and 4% in men (4), all those data show that OSAS is more common in acromegaly. Increased frequency of OSAS depends on a variety of anatomical changes leading to hyper-collapsibility of the posterior and lateral hypo-pharyngeal walls in acromegaly patients (14,17,18).

The relationship between disease activity of acromegaly and sleep apnea has been controversial. Some studies have demonstrated a positive correlation between GH and IGF-1 levels and AHI (16,19-24) whereas the others have not demonstrated any correlation (3,25,26). Another controversial subject is whether treatment of acromegaly (surgical or medical) has an effect on SAS severity. Previous studies have found variable results. Some studies have shown that SAS persisted despite of hormonal control of acromegaly after treatment (19,26,27). On the other hand, others have shown that SAS improved after hormonal control with effective treatment in acromegalic patients (20,21,28-30). Some investigators have believed that SAS is raised due to reversible and irreversible anatomical changes (17,18,31-33). Refractory SAS despite of acromegaly treatment may be caused by irreversible structural changes due to fixed hypertrophy and/or fibrosis of soft tissue and also bone deformity.

SAS in acromegaly patients must be treated mainly by CPAP like other SAS patients in general population. Nevertheless, acromegaly patients must be reassessed to adjust CPAP or to stop CPAP therapy after acromegaly treatment because reversible changes might eliminate the need for CPAP or might lead to change in appropriate CPAP pressure. The aim of the present study was to determine the prevalence of OSAS and risk factors associated with OSAS in acromegalic patients and correlation of disease activity with OSAS. Moreover, the effect of acromegaly treatment on OSAS is analysed to clarify if the treatment of acromegaly also cures OSAS in those group of patients.

## Materials and Methods

The study was performed on 15 patients with active acromegaly who were diagnosed and followed up by Endocrinology Department of Erciyes University Medical Faculty from December 2008 to March 2010. Patients were also evaluated for OSAS in Sleep Disorders Unit-Neurology Department of Erciyes University Medical Faculty. The local ethics committee approved the study protocol. The study was conducted in accordance with the declaration of Helsinki and local laws depending on whichever afforded greater protection to the patients. All the patients were gave their informed consent of participation in the study.

### Study Design

Patients were evaluated by polysomnography (PSG) recordings and hormone levels and MRI scans at the baseline. Polysomnography recordings and hormone studies were repeated 6 months after the surgery or/and medical treatment (Figure 1).

### Patients

Patients involved in the study were all newly diagnosed and have not received any medical or surgical treatment for acromegaly, previously. Acromegaly was biochemically diagnosed as the presence of increased IGF-1 levels according to age and sex and lack of GH suppression to less than 1 µg/L following a 75 g oral glucose load (Table 1). Oral glucose load was not performed on 2 patients because they were diagnosed as diabetes. Therefore, they were excluded from study. One patient died during the follow up period because of myocardial infarction. Therefore, the study was completed with 12 patients.

Remission was defined as having normal IGF-1 levels according to age and sex and suppressed GH  $\leq 1$  µg/L after OGTT or having a safe basal GH level (For the patients receiving Oct-LAR pre glucose GH value of OGTT was used).

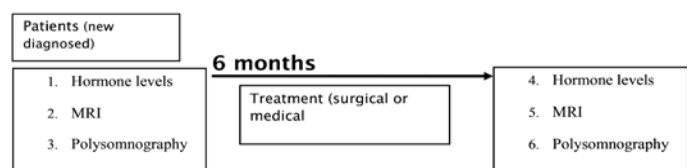


Figure 1. Summary of study design. Newly diagnosed acromegaly patients were evaluated at the baseline and 6 months after the treatment by means of hormone levels and sleep parameters including sleep apnea.

Blood samples were taken for growth hormone (GH), insulin-like growth factor-1 (IGF-1), follicle stimulating hormone (FSH), leutinizing hormone (LH), total testosterone (TT), free testosterone (FT), free thyroxine (FT4), free triiodothyronine (FT3), prolactin (PRL), estradiol (E2), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), cortisol levels from all patients. All serum samples were collected in the early morning after an 8 h fasting period. Neither pituitary deficiencies nor excessive hormone secretion except for GH/IGF-1 were present in the patients.

#### IGF-1 and GH Determinations

Serum concentrations of IGF-1, GH were measured by sensitive and specific immunoradiometric assays (Active Non-Extraction IGF-1 IRMA DSL-2800, and Active Growth Hormone IRMA DSL-1900, Diagnostics System Laboratories, Webster, Texas) (for IGF-1; intra-inter assay variation coefficients (CVs) 4.9%-5.1%; for GH; intra-inter assay CV 4.1%-8.7%).

The normal range of IGF-1 levels (mU/l) according to age (in years) for males and females are respectively: 18-24 years: 118-515 and 72-500; 25-29 years: 80-445 and 63-448; 30-34 years: 62-409 and 57-412; 35-39 years: 54-395 and 53-397; 40-44 years: 51-388 and 48-385; 45-49 years: 48-381 and 42-369; 50-54 years: 46-375 and 37-354; 55-59 years: 43-368 and 33-344; 60-64 years: 40-358 and 30-336; 65-69 years: 36-342 and 28-329;  $\geq 70$  years: 30-316 and 26-323 (34).

#### Polysomnography Recordings

Two polysomnography (PSG) recordings were performed on the patient group, one in the baseline period and the other at the sixth month of treatment (either surgery or medical). A full night PSG recording was composed of a computerized recording system (Somnostar Alpha®, Yorba Linda, CA, USA or Grass-Telefactor®, West Warwick, RI, USA) which consists of: 1) sleep monitoring through six-channel electroencephalography (EEG), 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 and a nasal cannula sensor for apnea-hypopnea detection, piezocrystal effort belts for thoraco-abdominal movement detection and a pulse oximeter. Sensors were placed and the equipment was calibrated at the Sleep Laboratory of the Erciyes University Hospital by a certified sleep technician. The sleep recordings were made from 23:00 to 07:00 h. All recordings were scored based on 30 s. epochs according to the American Academy of Sleep Medicine (AASM) 2007 PSG scoring criteria.

Sleep parameters were assessed based on the sleep recordings and included: 1) sleep efficiency (SE); the percentage of total sleep time with reference to time in bed; 2) sleep latency; the time between 'lights off' and the first occurrence of any sleep stage; 3) wake after sleep onset; the number of minutes of wake over initial sleep onset to final awakening; 4) the percentage and durations of different sleep stages with reference to total sleep time; 5) the apnea-hypopnea index (AHI), the number of apnea and hypopnea per hour of sleep. An obstructive apnea was defined as a flat oronasal signal accompanied by respiratory effort movement at least 10 s. A central apnea was defined as a flat oronasal signal accompanied by no respiratory effort movement at least 10 s. An obstructive hypopnea was defined

as 30% reduction in the oronasal signal and drop in oxygen saturation by at least 4% from the immediately preceding baseline accompanied by respiratory effort movement. The AHI was calculated and OSA or central apnea syndrome was defined according to the International Classification of Sleep Disorders (ICSD) 2; 6) periodic leg movement index (PLMI); which is defined according to the AASM criteria. The data were scored by a sleep medicine specialist who was masked to the status of the treatment regimen (pre vs. post treatment).

#### Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences version 15.0 for Windows system (SPSS Inc., Chicago, Illinois, USA). Changes in parameters pre- versus post-treatment (surgery and/or medical) were analysed using Wilcoxon signed rank test. Spearman correlation analysis was used to test the correlation between delta IGF and delta AHI and delta min O<sub>2</sub>sat. Results are given as median (min-max). All statistical tests were two-sided, and a p-value less than 0.05 was considered significant.

#### Results

Individual characteristics of the patients before the treatment (baseline) are summarized in Table 1. Eleven of the 12 patients had OSAS according to the ICSD2 (92%). When IGF1, GH levels and adenoma diameters were compared with AHI, there was no correlation between acromegaly severity and AHI.

Following treatment, there was a significant decrease in IGF-1 (1039 [397.0-1680.0] ng/ml at baseline vs. 334 [23.0-1102.0] ng/ml at follow-up; p=0.003). After the treatment period, 7 patients (58%) were in remission. Six of those patients had still OSAS in PSGs. Five of the patients were not in remission after the six months of follow-up. Among those patients, three had still OSAS.

In the whole group of patients, a significant increase in min O<sub>2</sub>sat levels (76.0 [49.0-89.0] at baseline vs 86.0 [51.0-92.0] at follow-up; p=0.019) was found. However, there were no significant changes in AHI compared with the measures at baseline 30.3 [3.6-102.5] vs after treatment 18.0 [3.2-120.2] (p=0.784). However, eleven patients had OSA at baseline, and AHI was found to be decreased below 5-h in two of them. There was no correlation between the difference in IGF-1 and differences in AHI and min O<sub>2</sub>sat levels.

Seven patients whose serum IGF-1 levels reached to normal reference ranges for age and gender were accepted in remission (35). Results of the clinical and PSG recordings of the patients in remission and are given in Table 2. Five patients were not in remission and those patients' pre- and post treatment clinical and PSG results are given in Table 3.

#### Discussion

Prevalence of OSAS in acromegaly patients is thought to be roughly 60%, changing between 19% and 93% (3,12-14). This large interval is thought to be the result of difference of study methods and diagnostic criteria. In our study, using 2007 AASM diagnostic criteria for OSAS, we found a quite high prevalence as 83% of moderate and severe OSA in acromegaly patients. Severity of OSAS is determined by AHI. If AHI is between 15-30, OSA is diagnosed as moderate. If AHI is above 30, OSA is

diagnosed as severe. In our study, after PSG recording, moderate or severe OSAS is diagnosed to 75% (9/12) of acromegaly patients. On the other hand, GH and IGF-1 levels are assessed as measure of severity of acromegaly. Any correlation between AHI and GH, IGF-1 levels was not determined. Therefore, GH and IGF-1 levels do not effect or are not unique parameters on OSAS severity. Results of studies incurred until the present day are contradictory. While some studies have shown positive correlation between AHI and GH, IGF-1 (16,19-24) the others

have not shown this correlation (3,25,26). Those results as well as some previous studies were not able to show any relationship between GH, IGF-1 levels and AHI have suggested that there are irreversible anatomical changes in acromegaly patients with OSAS during disease. Irreversible anatomical changes in soft and especially bone tissues were not recovered even if GH and IGF-1 levels are in normal limits after acromegaly treatment (17,18,31-33). On the other hand, in those studies it has been suggested that reversible changes have been recovered

**Table 1. Characteristics of the patients at baseline**

| Patient No | Age (years) | Sex | IGF-1 level (mU/l) | Nadir GH level after OGTT (µIU/ml) | Diameters of Pituitary adenoma (mm) | Treatment modality |
|------------|-------------|-----|--------------------|------------------------------------|-------------------------------------|--------------------|
| 1          | 38          | M   | 1275               | 5.10                               | 12                                  | Surgery            |
| 2          | 27          | M   | 1419               | 15.30                              | 43                                  | Surgery+SSA*       |
| 3          | 24          | M   | 1019               | 8.00                               | 10                                  | SSA                |
| 4          | 44          | M   | 1039               | 9.00                               | 11                                  | Surgery            |
| 5          | 30          | M   | 2042               | 1.20                               | 6                                   | Surgery            |
| 6          | 28          | F   | 4400               | 10.40                              | 36                                  | Surgery            |
| 7          | 61          | M   | 397                | 30.00                              | 26                                  | Surgery            |
| 8          | 40          | M   | 1305               | 4.10                               | 9                                   | SSA                |
| 9          | 46          | F   | 1329               | 2.70                               | 9                                   | SSA                |
| 10         | 66          | F   | 938                | 5.33                               | 12                                  | Surgery            |
| 11         | 44          | M   | 994                | 13.00                              | 12                                  | Surgery            |
| 12         | 29          | F   | 1680               | 16.00                              | 27                                  | Surgery+SSA        |
| 13         | 64          | M   | 966                | 11.04                              | 16                                  | Surgery            |
| 14         | 45          | F   | 1065               | 1.70                               | 15                                  | Surgery            |
| 15         | 55          | M   | 896                | 3.80                               | 12                                  | Surgery            |

\*: Somatostatin analogue

**Table 2. Clinical and PSG parameters of patients in remission**

| Patient no | BMI (kg/m <sup>2</sup> ) |                     | IGF-1 (ng/ml) |                     | AHI (n/hour) |                     | Min O <sub>2</sub> sat |                     |
|------------|--------------------------|---------------------|---------------|---------------------|--------------|---------------------|------------------------|---------------------|
|            | At baseline              | Following treatment | At baseline   | Following treatment | At baseline  | Following treatment | At baseline            | Following treatment |
| 2          | 32.3                     | 32.3                | 1039          | 201                 | 12.6         | 52.1                | 77                     | 71                  |
| 4          | 32.5                     | 31.6                | 1065          | 261                 | 102.5        | 120.2               | 50                     | 51                  |
| 5          | 27.0                     | 27.3                | 397           | 23                  | 65.1         | 48.6                | 70                     | 86                  |
| 6          | 28.4                     | 31.6                | 938           | 334                 | 27.2         | 4.6                 | 57                     | 79                  |
| 8          | 29.0                     | 28.4                | 2042          | 239                 | 8.1          | 32.2                | -                      | 84                  |
| 9          | 29.1                     | 28.4                | 966           | 263                 | 57.5         | 59.3                | 49                     | 76                  |
| 11         | 31.1                     | 33.2                | 1305          | 171                 | 56.2         | 16.7                | 66                     | 85                  |

**Table 3. Clinical and PSG parameters of patients not in remission**

| Patient no | BMI (kg/m <sup>2</sup> ) |                     | IGF-1 (ng/ml) |                     | AHI (n/hour) |                     | Min O <sub>2</sub> sat |                     |
|------------|--------------------------|---------------------|---------------|---------------------|--------------|---------------------|------------------------|---------------------|
|            | At baseline              | Following treatment | At baseline   | Following treatment | At baseline  | Following treatment | At baseline            | Following treatment |
| 1          | 27.6                     | 29.2                | 1680          | 740                 | 18.7         | 3.2                 | 89                     | 92                  |
| 3          | 21.5                     | 21.8                | 1019          | 1102                | 30.3         | 70.1                | 86                     | 86                  |
| 7          | 27.1                     | 27.8                | 896           | 366                 | 48.2         | 18.0                | 76                     | 91                  |
| 10         | 31.3                     | 31.9                | 1419          | 540                 | 3.6          | 4.4                 | 88                     | 90                  |
| 12         | 27.1                     | 25.3                | 1275          | 408                 | 16.4         | 16.6                | 82                     | 88                  |

when GH and IGF-1 levels are returned to normal ranges (36). Recovered anatomical changes will cause a decrease in AHI. All this condition is implied that relation between GH, IGF-1 and AHI is vary from one patient to another. In fact, disease severity in acromegaly is known to be related to disease duration rather than GH and IGF-1 levels (22-24).

Probably, duration of acromegaly is one of the most important factors in determining the soft and bony tissue changes. Unfortunately, it is quite difficult to accurately determine the onset of the disease either from patient history or laboratory evaluation. Patients generally refer to hospital with complications of disease.

Relation between GH, IGF-1 levels and AHI biochemically in remission or with active disease were again assessed at the sixth month of treatment. Severity of AHI were found to be unchanged in patients with and without remission. Also, there was not a statistically difference between AHI levels in baseline and 6 months after treatment. Therefore increased or decreased GH and IGF-1 levels do not seem to have a direct effect on AHI. Also, in previous studies, treatment modalities were not shown to cause any difference on AHI (17). Since all the patients were treated with surgery and only 2 of them received octreotide-LAR in addition to surgery and one of them was on primary octreotide-LAR treatment, it is difficult to comment on the effects of different treatment modalities.

Gold standard treatment of patients with mild and severe OSAS in general population is CPAP. CPAP is also almost always mandatory in acromegalic OSAS patients since OSAS in acromegaly patients cause or aggravate cardiovascular and metabolic complications. Refractory OSAS in acromegaly patients is defined as the presence of OSAS that persists despite biochemically remission and acromegaly treatment. Acromegaly patients with OSAS in our study group, CPAP therapy was started synchronously with acromegaly treatment and at sixth month of CPAP therapy, However CPAP treatment was with drawn 7 days before PSG recording. In other words, indication of CPAP therapy was still present. AHI was statistically indifferent in patients with or without remission.

In conclusion, in this study, it was determined that prevalence of OSAS in acromegaly is more frequent than general population. GH and IGF-1 levels which are indicators of active disease in acromegaly patients is not a good marker to determine severity of OSAS. Also, provided biochemically remission with acromegaly treatment (medical and/or surgery) was not found to be effective in reversing OSAS. OSAS is a condition negatively

affecting prognosis increased morbidity and mortality due to acromegaly. It is important to treat of acromegaly for OSAS at early period before irreversible anatomical changes emerge in acromegaly patients. If OSAS and its complications had been prevented, morbidity and mortality in acromegaly patients would have been decreased. On the other hand, OSAS in acromegaly patients should be treated by CPAP. Requirement for treatment continues in patients on remission, too. Therefore, acromegaly patients should be closely followed and be reassessed by PSG recording.

## References

- Melmed S. Medical progress: acromegaly. *N Engl J Med* 2006;355:2558-73.
- Kwon O, Song YD, Kim SY, Lee EJ; Rare Disease Study Group, Science and Research Committee, Korean Endocrine Society. Nationwide survey of acromegaly in South Korea. *Clin Endocrinol (Oxf)* 2013;78:577-85.
- Grunstein RR, Ho KY, Sullivan CE. Sleep apnea in acromegaly. *Ann Intern Med* 1991;115:527-32.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230-5.
- Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, et al. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry. *Eur J Endocrinol* 2004;151:439-46.
- Blanco Perez JJ, Blanco-Ramos MA, Zamarron SC, Souto Fernandez A, Mato Mato A, Lamela Lopes J. Acromegaly and sleep apnea. *Arch Bronconeumol* 2004;40:355-9.
- Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. *J Clin Endocrinol Metab* 2004;89:667-74.
- Holdaway IM. Excess mortality in acromegaly. *Horm Res* 2007;68 Suppl 5:166-72.
- Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, et al. Mortality in patients with pituitary disease. *Endocr Rev* 2010;31:301-42.
- Bresnitz EA, Goldberg R, Kosinski RM. Epidemiology of obstructive sleep apnea. *Epidemiol Rev* 1994;16:210-27.
- Hart TB, Radow SK, Blackard WG, Tucker HS, Cooper KR. Sleep apnea in active acromegaly. *Arch Intern Med* 1985;145:865-6.
- Weiss V, Sonka K, Pretl M, Dostalova S, Klozar J, Rambousek P, et al. Prevalence of the sleep apnea syndrome in acromegaly population. *J Endocrinol Invest* 2000;23:515-9.
- Buyse B, Michiels E, Bouillon R, Robbaers H, Demedts M. Relief of sleep apnoea after treatment of acromegaly: Report of three cases and review of the literature. *Eur Respir J* 1997;10:1401-4.



14. Rosenow F, McCarthy V, Caruso AC. Sleep apnea in endocrine disease. *J Sleep Res* 1998;7:3-11.
15. Perks WH, Horrocks PM, Cooper RA, Bradbury S, Allen A, Baldock N, et al. Sleep apnea in acromegaly. *Br Med J* 1980;280:894-7.
16. Rosenow F, Reuter S, Deuss U, Szellies B, Hilgers RD, Winkelmann W, et al. Sleep apnea in treated acromegaly: relative frequency and predisposing factors. *Clin Endocrinol (Oxf)* 1996;45:563-9.
17. Hochban W, Ehlenz K, Conradt R, Brandenburg U. Obstructive sleep apnea in acromegaly: the role of craniofacial changes. *Eur Respir J* 1999;14:196-202.
18. Dostalova S, Sonka K, Smahel Z, Weiss V, Marek J, Horinek D. Craniofacial abnormalities and their relevance for sleep apnea syndrome aetiopathogenesis in acromegaly. *Eur J Endocrinol* 2001;144:491-7.
19. Pekkarinen T, Partinen M, Pelkonen R, Iivanainen M. Sleep apnea and daytime sleepiness in acromegaly: relationship to endocrinological factors. *Clin Endocrinol (Oxf)* 1987;27:649-54.
20. Mickelson SA, Rosenthal LD, Rock JP, Senior BA, Friduss ME. Obstructive sleep apnea syndrome and acromegaly. *Otolaryngol Head Neck Surg* 1994;111:25-30.
21. Ip MS, Tan KC, Peh WC, Lam KS. Effect of Sandostatin LAR on sleep apnea in acromegaly: correlation with computerized tomographic cephalometry and hormonal activity. *Clin Endocrinol (Oxf)* 2001;55:477-83.
22. Sze L, Schmid C, Bloch KE, Bernays R, Brandle M. Effect of transsphenoidal surgery on sleep apnea in acromegaly. *Eur J Endocrinol* 2007;156:321-9.
23. Van Haute FR, Taboada GF, Correa LL, Lima GA, Fontes R, Riello AP, et al. Prevalence of sleep apnea and metabolic abnormalities in patients with acromegaly and analysis of cephalometric parameters by magnetic resonance imaging. *Eur J Endocrinol* 2008;158:459-65.
24. Davi MV, Dalle Carbonare L, Giustina A, Ferrari M, Frigo A, Lo Cascio V, et al. Sleep apnea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease. *Eur J Endocrinol* 2008;159:533-40.
25. de Boer H, Roelfsema F, Fröhlich M, Kamphuisen HA, van Seters AP. Plasma growth hormone profiles and sleep: a study of 13 treated patients. *Clin Endocrinol (Oxf)* 1989;30:251-61.
26. Pelttari L, Polo O, Rauhala E, Vuoriluoto J, Aitasalo K, Hyypä MT, et al. Nocturnal breathing abnormalities in acromegaly after adenomectomy. *Clin Endocrinol (Oxf)* 1995;43:175-82.
27. Cadieux RJ, Kales A, Santen RJ, Bixler EO, Gordon R. Endoscopic findings in sleep apnea associated with acromegaly. *J Clin Endocrinol Metab* 1982;55:18-22.
28. Main G, Borseley DQ, Newton RW. Successful reversal of sleep apnoea syndrome following treatment for acromegaly, confirmed by polygraphic studies. *Postgrad Med J* 1988;64:945-6.
29. Piper JG, Dirks BA, Traynelis VC, Van Gilder JC. Perioperative management and surgical outcome of the acromegalic patient with sleep apnea. *Neurosurgery* 1995;36:70-4; discussion 74-5.
30. Jaffrain-Rea ML, Minniti G, Moroni C, Esposito V, Ferretti E, Santoro A, et al. Impact of successful transsphenoidal surgery on cardiovascular risk factors in acromegaly. *Eur J Endocrinol* 2003;148:193-201.
31. Ferguson JK, Donald RA, Weston TS, Espinar EA. Skin thickness in patients with acromegaly and response to treatment. *Clin Endocrinol (Oxf)* 1983;18:347-53.
32. Isono S, Saeki N, Tanaka A, Nishino T. Collapsibility of passive pharynx in patients with acromegaly. *Am J Respir Crit Care Med* 1999;160:64-8.
33. Tolis G, Angelopoulos NG, Katounda E, Rombopoulos G, Kaltzidou V, Kaltsas D, et al. Medical treatment of acromegaly: comorbidities and their reversibility by somatostatin analogs. *Neuroendocrinology* 2006;83:249-57.
34. Bayram F, Tonyukuk GV, Demir O, Kaya A, Gundogan K, Emral R, et al. Epidemiologic survey: reference ranges of serum insulin-like growth factor 1 levels in Caucasian adult population with immunoradiometric assay. *Endocrine* 2011;40:304-9.
35. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, et al; Acromegaly Consensus Group. A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab* 2010;95:3141-8.
36. Gleeson K, Zwillich C, White D. Chemosensitivity and the ventilatory response to airway obstruction during sleep. *J Appl Physiol* (1985) 1989;67:1630-7.