Pituitary diseases: long-term clinical consequences

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Chapter 5

Somatostatin analog treatment is associated with an increased sleep latency in patients with long-term biochemical remission of acromegaly.

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ABSTRACT

Background

Somatostatin analogs induce alterations in sleep in healthy adults. Presently, it is unknown whether somatostatin analog treatment affects sleep parameters in patients with acromegaly.

Design

Case-control study.

Patients and measurements

We assessed sleepiness and sleep patterns in 62 adult patients (32 men, age 61 years (33-88 yrs) controlled by surgery alone or postoperative radiotherapy (69%), and/or somatostatin analogs (31%). We used two validated sleep questionnaires (Epworth sleepiness score and Münchener Chronotype Questionnaire). Patient outcomes were compared to controls.

Results

Sleep duration and timing of sleep were not different in patients compared to controls. However, sleepiness score was increased in all patients compared to controls: 6 (1-20) vs. 4 (0-14), p=0.014 (median (range)), reflecting increased daytime sleepiness. Snoring was reported in 68% of both patients and controls (p=0.996), observed apnoea's and restless legs in 23% and 37% of patients compared to 12% and 21% of controls (p=0.062 and p=0.031, resp.). In addition, sleep latency was increased in patients treated by somatostatin analogs compared to patients cured by surgery and/ or radiotherapy (52 ± 48 min vs. 26 ± 40 min, p=0.005), resulting in a delayed sleep onset (24:08 ± 1:26 h vs. 23:25 ± 0:43 h, p=0.053). Sleep duration was unaffected.

Conclusions

Daytime sleepiness is increased in a homogeneous cohort of patients in long-term remission from acromegaly. In addition, somatostatin analog treatment increases sleep latency and delays sleep onset in patients with long-term biochemical control of growth hormone overproduction without altering total sleep duration.

INTRODUCTION

The aims of treatment in active acromegaly are to relief the symptoms of growth hormone (GH) excess, to decrease mass effects, to restore metabolic alterations, and to reduce the increased mortality risk associated with active acromegaly (1). Somatostatin analog treatment alone or surgical treatment alone can reach these targets in only 50-70% of the patients. Fortunately, combinations of surgery, radiotherapy, and/or drug therapy (somatostatin analogs and/or GH receptor blockade drugs) are able to control disease activity in almost all patients (2-5).

Acromegaly is associated with sleep disorders, including sleep disordered breathing, such as snoring, and sleep apnoea syndrome. The prevalence of the sleep apnoea syndrome was found to be as high as 80% in patients with acromegaly (reviewed in (6)). Treatment of acromegaly by transsphenoidal surgery or somatostatin analogs has been consistently found to reduce this high prevalence of sleep apnoea syndrome (7-12). However, somatostatin per se may also adversely influence sleep, because in experimental studies, somatostatin and its analog, octreotide, altered sleep (13;14). In healthy elderly persons, somatostatin administered during the first half of the night decreased total sleep time and rapid eye movement sleep (REMS) and increased the time spent awake in the first sleep cycle (14). In rats, repeated injections of octreotide caused decreases in non-rapid eye movement sleep (NREMS) time and NREMS intensity (13). In healthy young male subjects octreotide decreased stage 4 NREMS and REMS during the first half of the night (15). Based on these observations, it is possible that somatostatin treatment in patients with acromegaly may also adversely affect sleep.

Therefore, the aim of this study was to compare sleepiness and sleep patterns between patients cured from acromegaly by transsphenoidal surgery and/ or radiotherapy and patients with biochemical control of GH excess during treatment with somatostatin analogs.

PATIENTS AND METHODS

Protocol

For the present study, consecutive patients visiting our outpatient clinic with adequate control of GH excess were screened for participation (n=95).

Inclusion criteria were:

1) biochemical cure after primary treatment by transsphenoidal surgery, and if necessary, by adjuvant postoperative treatment with radiotherapy and/ or somatostatin analogs.

2) biochemical control of GH excess after primary treatment with somatostatin analogs.

Exclusion criteria were:

1) growth hormone deficiency after treatment for acromegaly and treatment with recombinant human growth hormone started within the previous year (n=16).

2) serious illness limiting the completion of the questionnaires (n=3).

Thus, 76 patients were found eligible to participate in this study. Questionnaires were sent to their homes in prepaid envelopes. After 6 weeks, nonresponders received a reminder letter, and, thereafter, were contacted by telephone to encourage completion and return of the questionnaires.

Each patient was also asked to provide a healthy control person of comparable age and sex, who did not use any medication, to serve as a control group with a comparable socio-economic status. The control group was extended with controls derived from other studies in our center who were approached similarly (16).

Cure or biochemical control on somatostatin analogs was defined by normal serum IGF-I levels for sex and age and serum GH levels below 1.9 µg/l (≈5 mU/l) for all patients, and also by a normal GH suppression during oral glucose loading (<0.38 µg/l) only in the patients without somatostatin analog treatment. In patients on somatostatin anologs, mean GH levels were obtained from 5 samples obtained with an interval of 30 minutes between 9.00 and 11.00 h am. Octreotide long-acting repeatable (n=15, Novartis Pharma AG, Basel Switzerland) and lanreotide autogel (n=4, Ipsen Biotech, Paris, France) were used as somatostatin analogs.

Premenopausal women were defined as LH/ FSH deficient when secondary amenorrhoea was present for more than 1 year. Postmenopausal women were defined as LH/FSH deficient when gonadotrophin levels were below the normal postmenopausal range (LH<10 U/l and FSH<30 U/l). In men, LH/FSH deficiency was defined as a testosterone level below the reference range (8.0 nmol/l). TSH deficiency was defined as a total or free T4 level below the reference range. ACTH deficiency was defined as an insufficient increase in cortisol levels (absolute value <0.55 µmol/l) after a corticotrophin releasing hormone test or insulin tolerance test. If results were below the lower limit of the respective reference ranges, substitution with thyroxine, hydrocortisone or testosterone was started. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.

Six patients had a GH and prolactin secreting adenoma at diagnosis. Four of these patients were cured after surgery and 1 patient was cured after combined surgery and radiotherapy. One patient was still treated with dopamine agonists at the time of the present study (a 75 year old male patient treated by surgery alone for a GH and prolactin secreting tumor).

The study protocol was approved by the medical ethics committee of the Leiden University Medical Center, and all subjects returning completed questionnaires gave written informed consent for participation in the study.

Study parameters

Primary study-parameters were the results of the two sleep questionnaires. The results were linked to age and gender of the patients, treatment characteristics (somatostatin analog treatment and duration of cure).

Sleep questionnaires

Epworth sleepiness scale (ESS)

The ESS is a validated eight-item questionnaire. The subject is asked to rate his likelihood of falling asleep in a variety of commonly encountered situations (17). Scores range from 0 (the least sleepy) to 24 (the most sleepy). Scores equal to or above 10 are interpreted as increased daytime sleepiness (18). An additional set of questions evaluating the prevalence of snoring, observed apnoea's, and nocturnal restless legs was added to ensure a standardized clinical assessment.

Münchener chronotype questionnaire (MCQ)

The MCQ is a validated questionnaire aimed at assessing chronotype and sleep patterns (19;20). Patients are explicitly asked to describe their sleep behaviour under normal circumstances. The temporal structure of sleep is assessed separately for workdays and free days. Parameters on free days are regarded to reflect individual sleep patterns without social obligations and are therefore reported in this paper (19).

Sleep duration on free days (SD_F), sleep onset on free days (SO_F), and rise time (RT_F) are calculated from questions concerning sleep onset and awakening on days on which there are no work or social obligations. The midsleep on free days (MS_F: clock time halfway during sleep duration) is calculated from SO_F and RT_F (20). The sleep latency on free days (SL_F) can be calculated by SO_F and time at which a subject went to bed.

Since most chronotypes tend to accumulate a sleep dept on work days, which is compensated for on free days, midsleep on workdays (MS_C) was corrected for the confounder sleep debt as follows: $MS_C=MS_F-(0.5*SD_F-(5*SD_{working\ days}+2*\ SD_F)/7)$ (20). Since only 25 of our patients and 56 of our controls had a daytime job, this correction was performed only for those subjects (20).

Assays and normal values

GH levels were measured with a sensitive immunofluorometric assay (Wallac, Turku, Finland), specific for the 22-kDA GH protein and calibrated against WHO International Reference Preparation 80/505. The detection limit was 0.01 µg/l, and the inter-assay coefficient of variation was 2.0-9.0% en intra-assay coefficient of variation was 1.6-8.4% between 0.1 and 18 µg/l (for conversion of µg/l to mU/l, multiply by 2.6).

Serum IGF-I concentrations (ng/ml) were measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, USA). The intra-assay variation was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l, respectively. IGF-I is expressed as SD score, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals (21;22;22).

Statistics

Data are presented as mean ± SD unless specified otherwise. SPSS for windows version 14.0 (SPSS Inc., Chicago, IL) was used for data analysis. Differences were considered statistically significant at $p \leq 0.05$. We used unpaired T-tests in case of normal distribution and non-parametric Mann-Whitney tests for the ESS and in case of skewed distribution. Chi-square tests and linear regression analysis were performed, when appropriate.

RESULTS

Patient and treatment characteristics

Seventy-one of 76 (93%) patients returned the questionnaires on sleep characteristics. Nine patients of these 71 patients preferred not to participate. Thus, 62 completed questionnaires were received. The study-population (32 men) had a mean age of 61 years with a range of 33 to 88 years. No significant differences in age, gender and tumor-characteristics were found between the study-population, and the 14 patients who preferred not to participate or who did not return the questionnaires.

The patients were compared to 98 controls (40 men) were with mean age of 59 years (range of 31 to 83 years). Age and gender in the control group were not different from the studied acromegaly patients (p=0.425 and p=0.152, respectively, Table 1).

All patients were in biochemical remission of GH excess after (multimodality) treatment. Fifty-five patients (89%) were treated with primary transsphenoidal surgery, whereas 6 were primarily treated with somatostatin analogs and 1 patient was in remission after pituitary apoplexy. Thirty-five of those 55 patients (64%) who were treated with primary transsphenoidal

Table 5/1: Clinical characteristics of 62 patients with acromegaly.

		Patients (n=62)	Controls (n=98)	P-value
Age (mean, range (yrs))		60.7 (33-88)	59.3 (31-83)	0.425
Gender (M/F, n)		32 (52)/ 30 (48)	38 (40)/ 57 (60)	0.152
GH (µg/l)		0.6 ± 0.6		
IGF-I SD scores		0.4 ± 1.4		
Disease state (n(%))	Cured after surgery and/ or radiotherapy	43 (69)		
	Well-controlled (current use of somatostatin analogs)	19 (31)		
Radiotherapy (n(%))		11 (18)		
Duration of remission (mean, range (yrs))		15.1 (5-30)		

Data are presented as mean with range or number with percentage in parentheses. M males; F Females; yrs years.

Table 5/2: Clinical characteristics of 43 patients cured of acromegaly versus 19 patients well-controlled by somatostatin analogs.

	Cured (n=43)	Well-controlled (n=19)	P-value
Age (mean, range (yrs))	59.3 (33-88)	64.0 (43-79)	0.140
Gender (M/F, n)	26/ 17	13/ 6	0.036
GH (µg/l)	0.6 ± 0.6	0.6 ± 0.5	0.658
IGF-I SD scores	0.2 ± 1.4	0.8 ± 1.2	0.098
Radiotherapy (n(%))	7 (16)	4 (21)	0.650
Duration of cure (mean, range (yrs))	15.7 (5-29)	20.1 (7-35)	0.077

Data are presented as mean with range or number with percentage in parentheses. M males; F Females; yrs years.

surgery were cured. Eleven patients of those 55 patients had received additional radiotherapy, four of whom were also treated with somatostatin analogs to establish disease control. Nine of the 55 postoperative patients received additional somatostatin analogs without postoperative radiotherapy.

Thus, 43 patients were cured (69%) by surgery only or additional postoperative radiotherapy or apoplexy, whereas 19 patients were biochemically well-controlled (31%) with somatostatin analogs either as primary treatment (n=6) or after surgery (n=13) (Table 2). The mean duration of cure was 15 years (range 5 to 30 years). The mean serum GH concentrations were 0.6 ± 0.6 µg/l and the mean IGF-I SD scores were 0.4 ± 1.4 SD.

Five percent of patients had ADH deficiency, whereas ACTH deficiency and TSH deficiency were present in 11% and 21% of patients, respectively. Seven patients were treated with estrogen or testosterone because of LH-FSH deficiency (19% of men and 14% of premenopausal women).

Comparison between patients with acromegaly and controls

Sleep duration on free days (SD_F) was not different between patients and controls (7:33 ± 1:11 h vs. 7:23 ± 1:01 h, p=0.386). Sleep onset on free days, sleep latency on free days, midsleep on free days, rising time on free days, and corrected midsleep (SO_F, SL_F, MS_F, RT_F, and MS_C, respectively) were not different compared to controls as well (Table 3).

However, the Epworth Sleepiness Scale (ESS) score was increased in patients compared to controls: 6 (1-20) vs. 4 (1-14); p=0.014 (median (range)), indicating increased daytime sleepiness in patients.

Sixty-eight percent of both patients and controls reported snoring (p=0.996), whereas 23% of patients reported observed apnoea's compared to 12% of controls (p=0.062). In addition, restless legs were reported in 37% in patients compared to 21% in controls (p=0.031).

In our patients, no correlations could be found between any of the sleep pattern parameters (sleep duration, onset, rise time, latency or midsleep on free days) and sleepiness scores on the ESS.

Table 5/3: Sleepiness scores and subjective sleep patterns in patients cured from acromegaly compared to controls.

		Patients (n=62)	Controls (n=98)	P-value
ESS	Mean score (median (range))	6 (1-20)	4 (0-14)	0.014
	>10 (%)	20	12	0.187
MCTQ	Sleep onset on free days (clock time h:min ± SD)	23:39 ± 1:02	23:44 ± 1:12	0.604
	Sleep latency (minutes ± SD)	34.2 ± 43.8	27.2 ± 22.2	0.185
	Rising time on free days (clock time h:min ± SD)	7:12 ± 1:11	7:08 ± 1:03	0.755
	Sleep duration on free days (duration h:min ± SD)	7:33 ± 1:11	7:23 ± 1:01	0.386
	Midsleep on free days (clock time h:min ± SD)	3:25 ± 0:57	3:26 ± 1:01	0.901
	Corrected midsleep (clock time h:min ± SD, n=25 *vs.* n=56)	3:51 ± 1:03	3:42 ± 0:44	0.456

Data are presented as mean ± SD or as percentages and compared with independent samples T-test, non-parametric Mann-Whitney U-tests or Chi-square test, when appropriate.

Factors influencing sleep in patients with acromegaly

Age

No significant correlations were found between age and ESS score or between age and sleep pattern parameters in all studied patients.

Gender

In patients with acromegaly, sleep duration was longer in women than men (7:52 ± 1:17 h vs. 7:15 ± 1:01 h, p=0.044). Midsleep on free days (MS_F) was significantly different in women compared to men (clock time 3:41 ± 1:00 h vs. clock time 3:11 ± 0:51 h, p=0.009). This difference in MS_F was associated with a later rise time in women (7:37 ± 1:07 h in women vs. 6:49 ± 1:08 h in men, p=0.007). MS_C, SL_F, and ESS scores did not differ between men and women.

Duration of remission, GH concentrations and IGF-I SD scores

No significant correlations were found between GH, IGF-I concentrations or duration of remission and ESS score or between GH, IGF-I concentrations or duration of cure and sleep pattern parameters (sleep onset, rising time, sleep duration, and midsleep on free days).

Diabetes mellitus, BMI and smoking

Six patients (10%) suffered from diabetes mellitus. No differences were found between patients with type 2 diabetes mellitus (n=6, 10%) or patients without type 2 diabetes mellitus with respect to ESS score or sleep pattern parameters. Mean BMI was 27.1 ± 4.4 kg/m^2. No correlations between BMI and ESS scores or sleep pattern parameters were found. Twenty-five percent

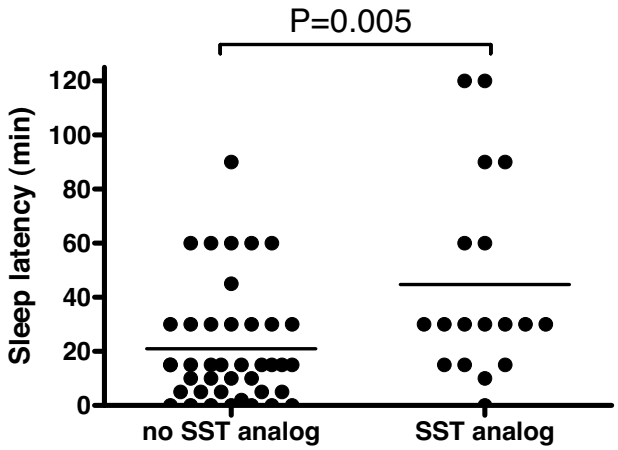

Figure 5/1: Sleep latency is increased in patients treated with somatostatin analogs (SST analog, n=19) compared to patients treated by surgery and or radiotherapy alone (no SST analog, P=0.005).

of patients were smokers. These patients were significantly younger than non-smokers (52.4 ± 10.7 years vs. 63.6 ± 10.4 years, p=0.001). Midsleep on free days, MS_F, was significantly later (4:02 ± 1:18 h in smokers vs. 3:13 ± 0:37 h in non-smokers, P=0.035) due to later sleep onset and rising time.

Cure versus biochemical control by somatostatin analogs

IGF-I SD scores and GH levels did not differ between the cured patients and the patients with biochemical control of acromegaly by somatostatin analogs. The percentage of patients previously treated with radiotherapy or the prevalence anterior pituitary deficiencies did not differ between the two groups as well. Sleep latency on free days was increased in patients biochemical control of acromegaly by somatostatin analogs (52 ± 48 min vs. 26 ± 40 min, p=0.005, Figure 1), which consequently delayed sleep onset (24:08 ± 1:26 h vs. 23:25 ± 0:43 h, p=0.053) and midsleep on free days (MS_F, clock time 3:50 ± 1:17 h vs. clock time 3:14 ± 0:41 h, p=0.022). Sleep duration of free days (SD_F) was unaffected (7:36 ± 1:11 h vs. 7:24 ± 1:11 h, p=0.540, Table 4). After exclusion of patients treated with radiotherapy and patients treated with primary somatostatin analogs, we could assess the difference between patients treated with primary surgery alone (n=36) and patients treated with primary surgery and subsequent somatostatin analogs (n=9). Sleep latency was increased in the latter group (p=0.050 in a non-parametric Mann-Whitney tests) resulting in a delay in sleep onset (24:21 ± 1:41 h vs. 23:24 ± 0:46 h, p=0.081), confirming the above analysis in all patients and pointing towards a somatostatin analog specific effect.

The percentage of smokers did not differ between those patients cured by surgery and/or radiotherapy (26%) and patients with biochemical control of acromegaly by somatostatin analogs (24%, p=09.869).

Table 5/4: Sleepiness scores and subjective sleep patterns in patients cured from acromegaly compared to patients with biochemically well-controlled acromegaly with somatostatin analogs.

		Cured (n=43)	Well-controlled (n=19)	P-value
ESS	Mean score (median (range))	6 (1-20)	7 (0-16)	0.571
	> 10 (%)	17	26	0.405
MCTQ	Sleep onset on free days (clock time h:min ± SD)	23:25 ± 0:43	24:08 ± 1:26	0.053
	Sleep latency (minutes ± SD)	26.2 ± 40.1	51.8 ± 47.5	0.005
	Rising time on free days (clock time h:min ± SD)	7:02 ± 1:03	7:33 ± 1:25	0.151
	Sleep duration on free days (duration h:min ± SD)	7:36 ± 1:11	7:24 ± 1:11	0.540
	Midsleep on free days (clock time h:min ± SD)	3:14 ± 0:41	3:50 ± 1:18	0.022

Data are presented as mean ± SD or as percentages and compared with independent samples T-test, non-parametric Mann-Whitney test or Chi-square test, when appropriate.

Stepwise linear regression analysis

Stepwise linear regression was performed in a model including age, gender, current use of somatostatin analogs, duration of cure, GH, and IGF-I concentrations as independent variables and ESS score, sleep duration on free days (SD_F), sleep onset on free days (SO_F), sleep latency on free days (SL_F), rise time on free days (RT_F), and midsleep on free days (MS_F) as dependent variables. Age, duration of cure, and IGF-I SD scores influenced neither sleep pattern parameters nor ESS scores. Sleep onset on free days (SO_F) was independently predicted by current use of somatostatin analogs (β=2929 (≈49 min), p=0.015) as was sleep latency (β=32.6 min, p=0.028). Rise time on free days (RT_F) was independently influenced by gender (0=Female, 1=Male, β=-3118 (≈-52 min), p=0.018).

DISCUSSION

The data in this study show that patients in long-term remission of active acromegaly experience increased daytime sleepiness compared to controls. Nonetheless, self-reported sleep patterns such as sleep onset or sleep duration did not differ from controls and were not correlated to increased daytime sleepiness scores. In addition, current somatostatin analog treatment induced an increase in self-reported sleep latency and consequently delayed sleep onset. Therefore, this study indicates increased daytime sleepiness despite adequate treatment of acromegaly and demonstrates that somatostatin treatment per se is associated with delayed sleep onset.

The Epworth sleepiness scores indicated increased daytime sleepiness in our patients and are comparable with scores found in another study in 6 patients with acromegaly six months after transsphenoidal surgery (8). In addition, the daytime sleepiness scores in our patients were comparable to scores found in patients treated for other pituitary tumors or cerebral diseases such as non-functioning adenomas (16), craniopharyngeoma (23), hypothalamic tumors (23), subarachnoid haemorrhage (24), or traumatic brain injury (25), indicative for the relationship between cerebral disease in general and increased daytime sleepiness.

In the particular group of patients with biochemical control of acromegaly, sleep apnoea could have contributed to the increased daytime sleepiness. Although not formally excluded, we did not find any significant differences in self-reported snoring or apnoea's. Although many reports have described the amelioration of sleep apnoea's after successful treatment of acromegaly (7-12), only one study in a homogenous cohort of patients cured from acromegaly reported the prevalence of sleep apnoea syndrome to be 20% (26). A detailed assessment of sleep apnoea syndrome in cured acromegaly is warranted even more since the introduction of GH receptor blockade therapy, which could further reduce tissue swelling and subsequently sleep apnoea syndrome in patients with acromegaly.

In addition, increased sleep latency, and consequently a delayed sleep timing, was found in patients on somatostatin analog therapy. In healthy elderly subjects, somatostatin impaired sleep especially by decreasing total sleep time and REMS, and by increasing the time spent awake in the first sleep cycle (14), although it did not influence sleep in young healthy adults (27). In rats, the long-acting somatostatin analog octreotide suppressed NREMS after repeated injections (13). Moreover, octreotide reduced stage 4 NREMS and REMS during the first half of the night and increased intermittent wakefulness during the second half of the night in young healthy adults (15). We could not identify polysomnographic studies of the effects of the depot preparations of octreotide or lanreotide on sleep parameters, which are interesting in the light of our results.

Growth hormone secretion during somatostatin analog treatment in acromegaly is not completely normalized (28), which is associated with altered diastolic function of the heart (29). From the current study, it becomes apparent that somatostatin analog treatment in itself also adversely affects sleep. Additional prospective polysomnographic studies with depot preparations, with or without GH receptor blockade drugs, are needed to further elucidate the effects of these drugs on sleep patterns and sleep quality in acromegaly even more since the primary treatment strategies are likely to change in the future.

Although the mechanism by which somatostatin impairs sleep is unknown, it is postulated to act at the level of the central nervous system. It has been proposed that somatostatin impairs GABAergic neuronal transmission in the sensory thalamus via presynaptic receptors in cats and rats (30), which could contribute to the observed decrease in NREMS after somatostatin administration (31). Growth hormone releasing hormone (GHRH) has been consistently found

to promote NREMS (31). Therefore, sleep seems to be under control of the same reciprocal interaction of GHRH and somatostatin that controls GH secretion.

Some factors may have influenced our results. Sleepiness and sleep patterns were assessed using self-reported questionnaires. The MCQ assesses sleep during free days and working days, but only at one occasion. However, a comparison of the data on sleep habits from the MCQ and data from a sleep log for 5 weeks by Roenneberg et al. demonstrated that sleep times obtained by both questionnaires on both workdays and free days were highly correlated ($p<0.0001$, (19)). Additionally, in the present study patients with acromegaly were compared to controls recruited by the patients. The advantage of using such controls is that they are from the same geographic area and socio-economic class as the patients (32). Although it is known that self-selected controls might be subject to selection bias, because patients might have chosen controls with a supposedly good health status (33), it is not likely that sleeping pattern plays any role in the choice for a specific control. Finally, based on the present results, the next step is to perform objective test of sleepiness and polysomnography to asses sleep quality and patterns in patients treated for acromegaly in more detail.

No relation was found between age and sleepiness scores. This is in contrast with findings in the general healthy population (34;35). This discrepancy is likely due to the limited range in ages of the subjects included in our study due to the generally older age of patients with acromegaly.

In conclusion, we found increased daytime sleepiness in patients cured from acromegaly despite normal sleep patterns and comparable prevalences of self-reported snoring and apnoea's. Treatment with somatostatin analogs is associated with increased sleep latency and, consequently, delayed sleep onset. Since somatostin analogs are the first choice for medical therapy of active acromegaly, additional studies are needed to assess sleep quality in order to identify the optimal treatment regimen not only with respect to therapeutic effects on disease activity, but also on the potential adverse effects on sleep.

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