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Does hormonal control obviate positive airway pressure therapy in acromegaly with sleep-disordered breathing?

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Summary
Introduction: Acromegaly is a disease in which uncontrolled release of growth hormone occurs after closure of epiphyseal plates, causing changes in the body that can lead to sleep disordered breathing (SDB). No definite guidelines regarding the treatment of SDB in acromegaly are available. In this study, we aimed to investigate the prevalence of SDB in acromegaly and whether hormonal control alters the necessity of positive airway pressure (PAP) therapy in acromegaly patients with SDB.
Methods: Forty-two acromegaly patients were included in the study and divided into two groups according to disease status, i.e., active or well controlled. All patients underwent polysomnography. Fourteen patients with active acromegaly were diagnosed with SDB and were evaluated for PAP therapy with polysomnography both before and 6 months after disease control was achieved.
Results: Sleep-disorder breathing was diagnosed in 22 of 42 patients, 7 of 20 patients with controlled-disease and 15 of 20 patients with active diseases. There were significant reductions in respiratory disturbance index (RDI), apnea index, desaturation index, central apnea number, and rapid eye movement-phase RDI at the control polysomnography. Initially, PAP therapy was indicated in 12 of 14 patients and PAP therapy indication held in 11 patients after acromegaly control was achieved.
Conclusion: Our study revealed that over half of patients with acromegaly had SDB. Furthermore, SDB severity decreases with acromegaly treatment; however, this decrease does not

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change the indication for PAP therapy; therefore, PAP therapy should not be delayed in acromegalic SDB patients.

Introduction

Sleep-disorder breathing (SDB) is a disease characterized by fragmented sleep and day-time sleepiness. There are many pathological components in its etiology. Although 27—80% of acromegaly patients have SDB, the rarity of acromegaly in the general population (2—4 cases/million) leads to an underestimated incidence [1—4]. Moreover, the leading cause of death in acromegaly is cardiovascular complications, and there is a definite relationship between SDB and cardiovascular diseases in patients with acromegaly [1].

Growth hormone (GH) and insulin-like growth factor-1 (IGF-I) are essential for the regulation of metabolism and body composition. Uncontrolled release of growth hormone after closure of epiphyseal plates leads to asymmetrical growth and bizarre hormonal changes in the body, particularly facial bone changes, edema, and hypertrophy of the upper airway mucosa, growth of the pharyngeal and laryngeal cartilages, nasal polyps, and increased size of the tongue; these can trigger obstructive sleep apnea syndrome (OSAS) [1—4]. Also, increased growth hormones and changes in the somatostatinergic system can lead to central sleep apnea syndrome [4].

The association between hormone activity level (GH/IGF-I) and SDB is controversial. Some studies have shown convincing data regarding the relationship between SDB frequency and disease activity (GH/IGF-I activity) in active acromegaly patients [5—9]. Some studies indicate an association between disease activity and central sleep apnea syndrome prevalence [10], but others reported no such association [11]. In the literature, OSAS is markedly more prevalent than central sleep apnea syndrome in acromegaly patients [5,6,12].

Although the relationship between acromegaly and SDB is well known, the effect of acromegaly control on the course of SDB is controversial [1,3,5,11]. It is postulated that if the acromegaly can be controlled, central sleep apnea syndrome and OSAS, due to hormonal and structural changes, will regress. However, some studies have shown that, due to permanent structural changes, SDB can remain even after complete hormonal treatment of acromegaly [1,7,13]. The efficacy of hormonal control in the treatment of SDB due to acromegaly is unclear, and no study has investigated the necessity of positive airway pressure (PAP) therapy after hormonal control.

In this study, we aimed to investigate the prevalence of SDB in active and controlled acromegaly patients and determine whether hormonal control alters the necessity of PAP treatment in acromegaly patients with SDB.

Patients and methods

Forty-two acromegaly patients who attended the Bezmialem Vakif University Endocrinology department between 1st January 2010 and 31st December 2012 were included in the study. Patients were divided into two groups according to disease status: active disease ($n = 22$) and controlled disease ($n = 20$). The active disease group consisted of newly diagnosed naive cases ($n = 15$) and uncontrolled patients ($n = 7$) who were diagnosed previously but whose disease was unable to be controlled with ongoing therapy. Patient selection and study phases are shown in Fig. 1. All patients underwent full night polysomnography. Fifteen of the 22 uncontrolled group patients were diagnosed as SDB and they were evaluated for PAP treatment according to the "American College of Chest Physicians Sleep Medicine Board Review: 4th edition" [14]. Of the 22 uncontrolled group patients, 7 had normal polysomnography results and were thus considered not to have SDB. They were discarded from follow-up (Fig. 1). Adults with moderate-to-severe OSAS must meet one of the following apnea-hypopnea index (AHI) criteria: A) AHI $\geq$15 events per hour, with or without symptoms; or B) AHI $\geq$5 events per hour and $\leq$14 events per hour, with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders, or insomnia, documented hypertension, ischemic heart disease, or history of stroke. One acromegaly patient with SDB left the study for personal reasons. Disease activity in the active disease group was controlled with medical treatment (cabergalin, lanreotid acetate, pegrisomant, and octreotide), surgery or radiotherapy, or with combinations of these. Fourteen patients were observed for 6 months after disease control was achieved without any treatment for SDB, and had control polysomnography. Median duration for achieving hormonal control was 8 months.

The procedures were in accordance with the guidelines of the Helsinki Declaration on human experimentation. Informed consent was obtained from all subjects. The study protocol was approved by the Institutional Ethics Committee.

Hormone assays

The diagnosis of acromegaly is made on the typical appearance of the patient and serum IGF-I or/and without suppression of GH $<$1 ug/l to an oral glucose tolerance test [15]. Blood GH and IGF-I levels were assayed using a chemiluminescence immunometric assay (Siemens Advia-Centaur USA). Age-related reference ranges for IGF-I were as follows: *18—20*: 197—956; *20—23*: 215—628; *23—25*: 169—591; *25—30*: 119—476; *30—40*: 100—494; *40—50*: 101—303; $>$*50*: 78—258. The cut-off level for GH was 2 ng/ml. The criteria for absence of clinical activity were normal levels of IGF-I, taking into account age and sex and a GH nadir value less than 1 μg/l [15].

Polysomnography evaluation

A Compumedics E 3142 polysomnography device was used (Compumedics Inc., Melbourne, Australia) for polysomnography, and findings were evaluated based on the

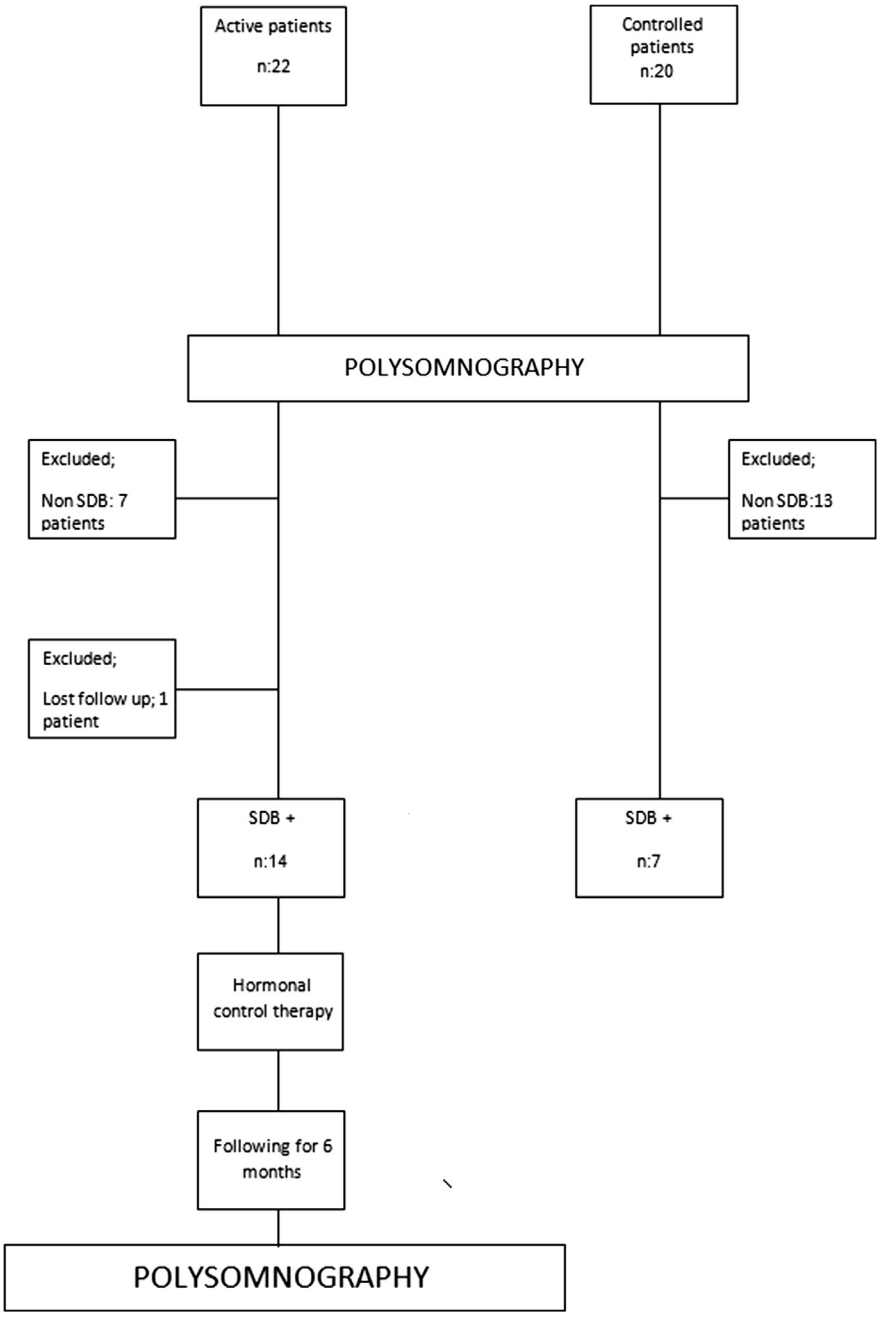

Figure 1 Flow chart of study.

guidelines published by the American Academy of Sleep Medicine in 2007 [16]. The respiratory disturbance index (RDI) was calculated by dividing the total number of episodes of apnea, hypopnea, and respiratory-related arousals by the total sleep time. Apnea was defined as complete cessation of airflow for $\geq$10 s. Hypopnea was defined as a reduction of more than 50% of three respiratory signals, airflow signals, or either respiratory or abdominal signals of respiratory inductance plethysmography, with an associated decrease of $\geq$3% in oxygen saturation or an arousal. OSAS was defined as an AHI of $\geq$5 with associated symptoms (sleep attacks or excessive daytime sleepiness), unsatisfying sleep, fatigue or insomnia, or heavy snoring and/or breathing pauses reported by the subject's partner), or an AHI $\geq$15 regardless of associated symptoms [16]. Patients were considered to have rapid eye movement (REM) related SDB if they met the following criteria: age $\geq$18 years, AHI $\geq$5, non-REM AHI $<$15, REM AHI to non-REM AHI ratio $>$2, and, total time spent in REM of $>$10 min [16]. The polysomnography data were reviewed by two investigators (MEA, and HKO).

Statistics

All statistical analyses were performed using the commercially available SPSS v.16.0 software package (SPSS Inc., Chicago, IL, USA). The results are presented as medians and

Table 1 Demographic and anthropometric parameters, co-existing diseases and treatment types.

		Controlled $n = 20$	Active $n = 22$	All cases $n = 42$
Male gender		7 (35)	11 (50)	18 (43)
Age, years		41 (33–44)	41 (37–57)	41 (35–41)
Body mass index (kg/m^2)		29 (25.2–33.5)	30 (27–32.2)	31 (31–33)
Epworth sleepiness scale		4.5 (2–11)	6 (3–9.2)	5 (2–10)
Neck circumference, cm		37.5 (34.5–42)	39 (35.5–43)	39 (34–43)
Waist circumference, cm		96.5 (91.2–106)	97 (89–106)	97 (90–106)
Growth hormone, ng/ml		0.78 (0.35–1.71)	3.35 (1.6–8.1)	1.57 (1.15–6.18)
IGF-I, ng/ml		229 (170–289)	709 (533–1025)	617 (478–752)
Smoking	Current	3 (15)	6 (27)	9 (21)
	Former	8 (40)	5 (23)	13 (31)
	Never	9 (45)	11 (50)	20 (48)
Diabetes mellitus		2 (10)	6 (27)	8 (19)
Hypertension		5 (25)	6 (27)	11 (26)
Coronary artery disease		0	2 (9)	2 (5)
Treatment	Surgery	–	5 (23)	7 (17)
	Medical	–	4 (18)	4 (10)
	Medical + surgery	–	12 (54)	22 (52)
	Medical + surgery + radiotherapy	–	1 (4)	9 (21)

Data are presented as numbers (percentages) or medians (25th–75th percentile). Abbreviations: ESS; Epworth sleepiness scale, IGF; insulin-like growth factor.

quartiles. Descriptive variables are given as percentages. The Mann–Whitney *U* test was used to compare the continuous parameters of SDB and non-SDB patients. The chi-square test was used to compare non-parametric variables. The Wilcoxon signed-rank test was used to compare the first and control polysomnography parameters.

Results

SDB was diagnosed in 22 of 42 patients. In subgroup analysis, 7 of the 20 patients with controlled disease and 15 of 22 patients with active disease had SDB. There were no significant differences in demographic and anthropometric measurements between the groups (Table 1). In the active acromegaly patients, the median (25th–75th percentile) time to control the disease activity was 8 (5–12) months. In the controlled disease group, duration of under remission was significantly higher in the non-SDB group compared to the SDB group: 21.5 (10–97) vs. 27 (16–84) months, respectively.

Age, treatment duration, and neck and waist circumferences were significantly higher in the SDB diagnosed group compared to the non-SDB group (Table 2). Median (25th–75th percentile) IGF-I levels of the SDB-diagnosed group and the non-SDB group were 316 (191–533) and 649 (246–795), respectively ($p > 0.05$). According to the polysomnography results, severity of SDB was as follows: 7 mild, 4 moderate, and 11 severe patients.

Fourteen active (naive and uncontrolled cases) acromegaly patients underwent control polysomnography 6 months after complete control, and significant reductions in RDI ($p = 0.004$), apnea index ($p = 0.014$), desaturation index ($p = 0.023$), total central apnea number ($p = 0.037$), and REM RDI ($p = 0.003$) were identified (Table 3).

Except one patient RDI levels were decreased in all patients at control polysomnography. Despite the reduction in RDI, there was no change in the severity of SDB in five patients. However, three patients became SDB free after treatment of acromegaly (Fig. 2A). Also, REM RDI and central apnea index significantly decreased at control polysomnography (Table 3, Fig. 2B, C).

Table 2 Comparison of sleep disorder parameters between patients with non-SDB and those with SDB.

	Non-SDB $n = 20$	SDB $n = 22$	p
Male gender	4 (20)	14 (64)	0.004
Age, years	36 (38–41)	50 (38–58)	0.001
Duration between symptom to diagnosis, years	5 (3–8)	5 (3–7)	NS
Treatment duration, months	6.5 (3–8.7)	25 (6.5–60)	0.002
Growth hormone, ng/ml	1.37 (0.67–3.35)	1.77 (0.99–5.98)	NS
IGF-I, ng/ml	316 (191–533)	617 (244–838)	NS
Epworth sleepiness scale	5 (2–8)	6 (3–11)	NS
Body mass index, kg/m^2	29 (26–33)	31 (27–35)	NS
Neck circumference, cm	36.5 (34–39)	42 (38–44)	0.003
Waist circumference index, cm	94 (92.25–99)	99 (93–108)	0.038

Data are presented as numbers (percentages) or medians (25th–75th percentile).
Abbreviations: SDB; sleep-disorder breathing, IGF; insulin-like growth factor.

Table 3 Comparison of before treatment and control polysomnography and anthropometric parameters of active acromegalic patients with SDB.

	$n = 14$		
	Before treatment	After treatment[a]	p
RDI	31.5 (14.4–38.3)	24.6 (12.4–31.4)	0.004
Body mass index	31 (28–36)	31.5 (28–34)	NS
Growth hormone, ng/ml	3.57 (1.59–8.15)	1.16 (0.8–1.39)	0.003
IGF-I, ng/ml	718 (605–1023)	137 (124–184)	0.001
Apnea index	17.7 (4.7–27.1)	12.8 (5.5–24.5)	0.014
ESS	6.5 (4–11)	5.5 (3–7.2)	NS
Hypopnea	11.2 (6.47–14.3)	9.8 (5.5–12.6)	NS
Lowest oxygen saturation	81.5 (75–86)	86 (81.7–89.7)	0.006
Desaturation index	5 (4–6.2)	4 (1.7–6)	0.023
Central apnea	3 (1–12.2)	1 (0–7.2)	0.037
REM-RDI	24.3 (14.1–45.9)	7.8 (1.2–17.2)	0.003
Neck circumference, cm	41 (38–43)	41 (38–43)	NS
Waist circumference, cm	100 (93–108)	99 (94–106)	NS

Data are presented as medians (25th–75th percentile).
Abbreviations: SDB; sleep-disorder breathing, RDI; respiratory disturbance index, IGF; insulin-like growth factor, ESS; Epworth sleepiness scale, REM-RDI; rapid eye movement phase-respiratory disturbance index, NS; not significant.
[a] After treatment indicates 6 months after hormonal remission via medical, surgical or radiotherapy or combined.

PAP therapy was indicated in 12 of 14 patients at first polysomnography, and was indicated due to AHI >15 in 10 patients and AHI <15 but with accompanying comorbidities, such as diabetes mellitus, coronary artery disease and hypertension, in two patients. The indication for PAP therapy abided at the control polysomnography of 11 patients, even after acromegaly control was achieved. At the control polysomnography, one patient showed a reduction in AHI to 13, but PAP remained indicated due to diabetes and coronary artery disease diagnoses.

Discussion

Our data revealed that more than half of the patients with acromegaly had SDB, and that the severity of SDB decreases with acromegaly treatment but that PAP therapy remains indicated even after treatment.

Due to the rarity of acromegaly in the general population, few studies with small group sizes have investigated the optimum treatment of SDB in acromegaly. Additionally, no studies have examined the effect of acromegaly treatment on PAP therapy, which is the essential treatment for SDB. Given this, should we plan SDB treatment independent of acromegaly treatment or should we wait until after acromegaly treatment? There are also no data regarding the necessity of PAP therapy in conjunction with acromegaly treatment, but American college of Chest Physicians Sleep Medicine Board Review advice to respiratory specialist to remain vigilant for evaluating the patients for PAP therapy [14].

Davi et al. studied 18 patients with controlled disease and 18 with uncontrolled disease, and found SDB prevalences of 56% and 39%, respectively [3]. However, SDB was more prevalent in the controlled disease group compared to the normal population (2–4%) [17,18]. Some studies have shown that SDB does not completely regress in acromegaly patients if permanent structural changes have occurred [5,13,19,20]. Our data suggest that the incidences of SDB in both controlled and uncontrolled patients are higher than in the normal population.

Obstructive sleep apnea is more common in acromegaly patients [7–9]. Our results are also similar to the literature. We found no relation between having SDB and serum IGF-I levels. The difference between the median serum IGF-I levels of our SDB and non-SDB patients (649 and 316, respectively) was not statistically significant, but a study with a larger group of patients may show otherwise. Among naive patients, central sleep apnea was found in one with uncontrolled disease and one with controlled disease.

Acromegaly patients have structural changes in the oropharyngeal soft tissues that have been shown to facilitate development of SDB. Decrease in the size of the uvula and tongue and regression of SDB after hormonal control have been reported [1,3,21–23]. Regression of SDB is likely due to normalization of the soft tissue structures, but permanent bone changes preclude complete regression of SDB. In our study, all but one patient had decreased RDI scores at the control polysomnography. Additionally, there were significant reductions in the central apnea and desaturation indices, which are related to SDB complications. SDB disappeared in only 2 of 14 cases but PAP treatment was already not indicated in these patients. Berg et al. reported that respiratory disturbance index was decreased from 23 to 18 after 6 months of medical treatment [5]. Also, Sze et al. showed RDI reduction from 41 to 11 after transsphenoidal surgery [1]. Other studies also reported no regression or complete regression of SDB after treatment [21–23]. RDI was decreased from 31 to 24 in our study.

Berg et al. [5] showed a significant positive correlation between the IGF-I level, tongue size, and BMI, but no correlation between the IGF-I level and RDI. Although we did not examine the upper airways of our patients, their neck and waist circumferences were significantly larger than in

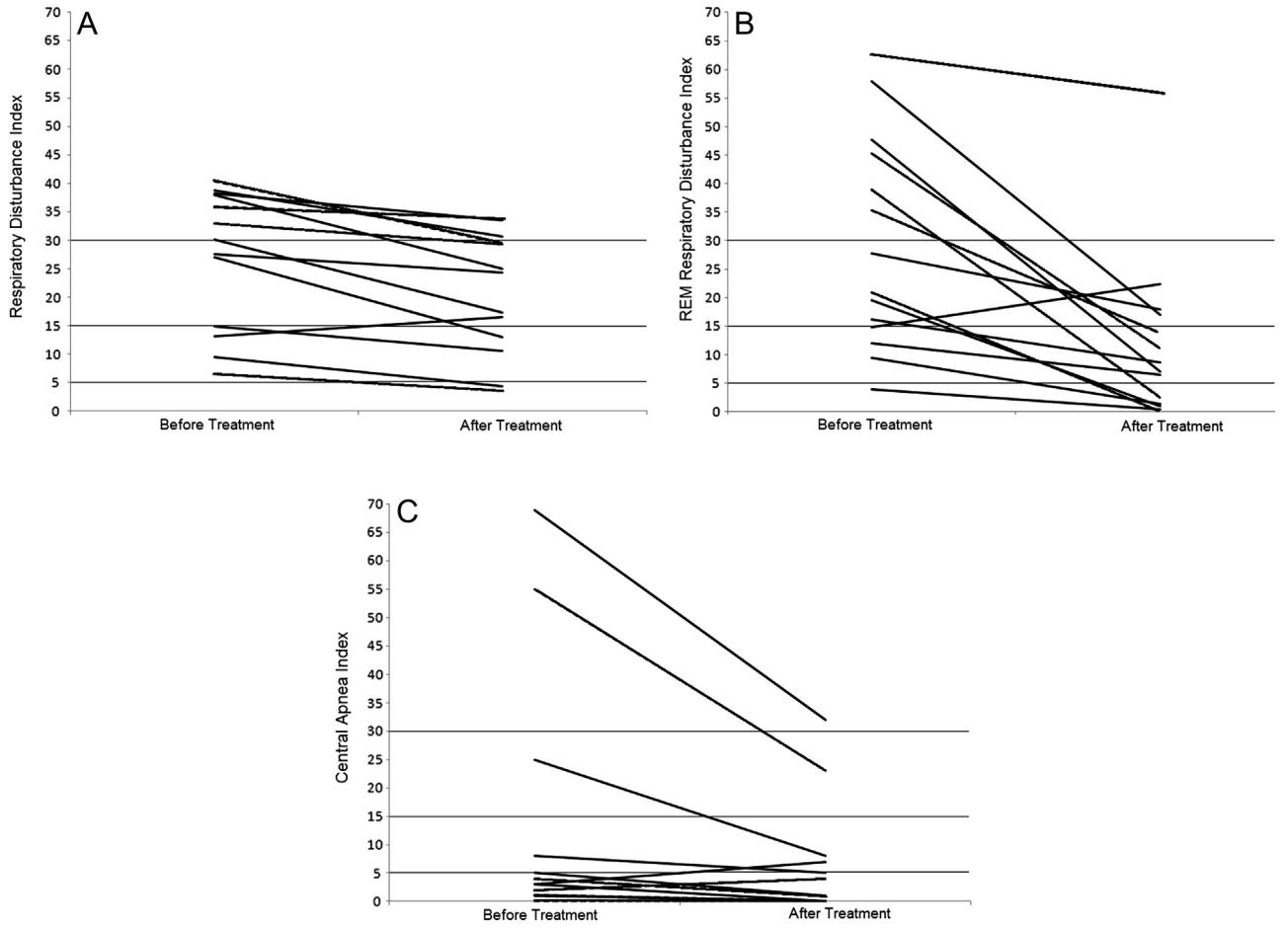

Figure 2 A — Comparison of respiratory disturbance index levels of at polysomnography before treatment and control, B — Comparison of REM-Respiratory disturbance index levels of at polysomnography before treatment and control, C — Comparison of central apnea index levels of at polysomnography before treatment and control.

the non-SDB group. Similar to the findings of Berg et al., RDI reduced despite no change in BMI and neck circumference in our study. These findings support that hormonal withdrawal reduces SDB severity without altering the BMI and neck circumference. However, in the study by Ip et al. [12], radiological cephalometric analysis showed reduced size of soft tissues, consistent with previous reports.

The aim of our study was to determine whether or not hormonal control therapy reduces the need for PAP therapy. Some previous studies as well as the American College of Chest Physicians Sleep Medicine Board Review: 4th edition [14] reported improvement in SDB with medical treatment. For this reason, we delayed initiating PAP therapy until after medical hormonal control therapy.

In our study, treatment of acromegaly improved the severity of SDB but did not reduce the need for PAP therapy. Thus, treatment of acromegaly has a limited effect on the improvement of SDB.

Six months of acromegaly remission can be considered a short time interval to observe possible changes in SDB. However, Ip et al. [12] and Berg et al. [5] showed that a 6-month remission of acromegaly is sufficient to observe predicted upper airway changes and improvement in sleep parameters. In our study, patients were followed for 14 months (8 months for treatment, 6 months for acromegaly remission) without any treatment for PAP and at the end of the follow-up the need for PAP treatment was not reduced.

It is obvious that large numbers of patients are needed to demonstrate alterations in the requirement for PAP therapy. However, acromegaly is a rare disease and studies of this condition have small numbers of patients or are retrospective in design. Although we had relatively small group size, cohort design and evaluating PAP indication before and after acromegaly treatment are main strengths of our study.

Male gender and age are reported as risk factors for SDB in acromegaly patients [24—26] which was consistent with our results. In literature, disease duration was reported to be associated with SDB frequency [1] but in our study estimated disease duration was similar in SDB and non-SDB group. However, the treatment duration was significantly longer in SDB patients. This discordance could be associated with the fact that the disease period is based on the patients' estimation and cannot be validated. The association between the treatment period and presence of SDB was considered to be more accurate. In the controlled group also, duration under remission is longer in the SDB group compared to the non-SDB group.

In conclusion, acromegaly patients were found to have a higher incidence of SDB than the general population. Although acromegaly treatment alone can improve the

severity of SDB, this is a limited effect and the requirement for PAP was not altered. Our findings suggest that although hormonal therapy can improve SDB, PAP treatment should be initiated concomitantly, if indicated.

Conflict of interest statement

We hereby declare that we have no conflict of interest related to the manuscript "Does hormonal control obviate positive airway pressure therapy in acromegaly with sleep-disordered breathing?".

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