

Prevalence of sleep apnea and lung function abnormalities in patients with acromegaly

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ABSTRACT

Background: Sleep apnea (SA) is highly prevalent in acromegaly. Ethnicity influences the prevalence of SA in the general population. We studied the prevalence of SA and other respiratory comorbidities in North Indian patients with active acromegaly. **Design:** Prospective, observational. **Materials and Methods:** Consecutive adult patients with active acromegaly ($n = 35$, age 39.7 ± 13.2 years) and hypersomatotropism (nonsuppression of serum growth hormone after oral glucose and elevated serum insulin-like growth factor-1 [IGF-1]) were evaluated for respiratory symptoms, scoring for SA (Epworth Sleepiness Score [ESS] and STOP-BANG), pulmonary function tests (PFT), high-resolution computerized tomography (HRCT) of the thorax, polysomnography (PSG), and transthoracic echocardiography. Age- and sex-matched healthy individuals ($n = 34$) served as controls. **Results:** Acromegaly subjects had dyspnea (34%), cough (37%), excessive daytime somnolence (43%), and fatigue (49%). Clinically significant ESS (>10) and STOP-BANG score (≥ 3) were present in 41% and 68.6% of subjects, respectively. PFT showed restrictive and obstructive patterns in 45.7% and 11.4% of acromegalics respectively; with higher total lung capacity (TLC), thoracic gas volume (TGV), and residual volume (RV). PSG revealed significantly higher SA events in acromegalics (central [acromegaly 24.63 ± 37.82 vs. control 3.21 ± 5.5], mixed [11 ± 19.46 vs. 3.50 ± 5.96], obstructive [34.86 ± 44.37 vs. 9.71 ± 10.48], and mean apnea-hypopnea index [AHI] [16.91 ± 18.0 vs. 7.86 ± 7.84]). Acromegalics had significantly higher prevalence of obstructive SA (71.4% [mild 31.4%, moderate 20%, severe 20%]) as compared to controls (38.2%). There was no correlation of AHI with serum IGF-1 and disease duration. **Conclusion:** Acromegaly subjects have a significantly higher prevalence of respiratory symptoms, SA, and abnormalities in PFT. Screening for respiratory comorbidities should be routinely recommended in all patients with acromegaly.

KEY WORDS: Acromegaly, polysomnography, pulmonary function tests, sleep apnea

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Submitted: 16-Mar-2021 Accepted: 20-Jun-2021 Published: 28-Dec-2021

Access this article online	
Quick Response Code: 	Website: www.lungindia.com
	DOI: 10.4103/lungindia.lungindia_182_21

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How to cite this article: Hashim Z, Gupta M, Nath A, Khan A, Neyaz Z, Tiwari S, *et al.* Prevalence of sleep apnea and lung function abnormalities in patients with acromegaly. Lung India 2022;39:58-64.

INTRODUCTION

Acromegaly is a rare endocrine disease characterized by the hypersecretion of autonomous growth hormone (GH) and elevated insulin-like growth factor-1 (IGF-1) levels, usually due to a pituitary adenoma. Tumoral GH hypersecretion leads to complications involving cardiovascular, respiratory, musculoskeletal, neurological systems.^[1] The cardiovascular complications resulting from a higher prevalence of hypertension, secondary diabetes, and dyslipidemia lead in higher mortality and morbidity.^[1] Respiratory complications are seen in about one-fourth of patients with acromegaly, with an estimated risk of mortality from the respiratory disease being 1.85 times higher than the general population.^[2] The associated respiratory co-morbidities include sleep-related breathing disorders, generally represented by sleep apnea (SA), and respiratory insufficiency. SA, the phenomenon of recurrent cessation or reduction of airflow to the lungs during sleep, is a common cause of snoring and daytime sleepiness in acromegaly. Various studies have reported a high prevalence of SA syndrome (SAS; 40%–80%) in patients with active acromegaly, two-third being obstructive form and one-third being central in origin.^[3,4] Attal and Chanson found an average rate of 69% for obstructive SA (OSA) in acromegalics with active disease.^[5] Independent predictors of OSA in acromegaly include disease activity, older age, and greater neck circumference. SA has been found to co-exist in both active and cured acromegaly subjects.^[6]

Factors such as race, ethnicity, body size, and body mass index (BMI) influence the prevalence of SA^[7] as well as affect the pulmonary functions,^[8] in the general population. The Indian subjects, as compared to Caucasians, have a smaller body frame size, narrower thoracic height, have lower forced vital capacity (FVC) (20%–24% lower in men, 25%–28% in women), and forced expiratory volume in one second (FEV1) (16%–23% in men, 20%–26% in women).^[9] Besides, South-East Asian ethnicity has been associated with increased risk of SA and the development of OSA at significantly lower BMI than Caucasians.^[10,11]

There is scant information about respiratory functions and the prevalence of SA in Indian patients with acromegaly. In our study, we assessed the pulmonary functions, polysomnography (PSG) findings, radiological characteristics, and cardiac functions in subjects with active acromegaly and compared them with age- and gender-matched healthy controls.

MATERIALS AND METHODS

Thirty-five consecutive patients, (17 men, 18 women) with active acromegaly were evaluated for respiratory comorbidities over a period of 3 years. The diagnostic criteria for the acromegaly included clinical features of acromegaly, lack of suppression of GH to 0.4 µg/L following an oral 75g glucose tolerance test, and elevated

serum IGF-1 levels for age- and gender-matched healthy subjects. Patients with confirmed biochemical parameters underwent gadolinium-enhanced magnetic resonance imaging of sella and suprasellar structures to define the tumor size and its extent. Patients meeting our inclusion criteria were enrolled in our study after their written informed consent. Exclusion criteria were ischemic heart disease, untreated hypo- or hyperthyroidism, and hypocortisolism, excess alcohol consumption, chronic liver or renal dysfunction, psychiatric illness, malignancy, pregnancy, and age below 18 years. The study protocol was approved by the Institute Ethics Committee (Ethics Cell No. 2017-170-EMP-99[B]). A group of 34 age- and gender-matched healthy subjects (19 men, 15 women) served as healthy, nonacromegaly controls.

A detailed clinical history and physical examination with emphasis on various symptoms and signs of acromegaly were performed in each patient. Anthropometry included measurement of height, weight, and calculation of BMI. All the subjects were screened for SA by STOP-BANG score and the Epworth Sleepiness Score (ESS). We enquired about the questions of excessive daytime sleepiness (EDS) by ESS score. A score of 11 and above was considered significant (0–5: Lower normal, 6–10: Higher normal, 11–12: Mild excessive, 13–15: Moderate excessive, 16–24 severe EDS). All the subjects were also enquired for various parameters of the STOP-BANG questionnaire. This questionnaire included eight dichotomous items (snoring, tiredness, observed apnea, high blood pressure, BMI (>35 kg/m²), age (>50 years), neck circumference (male >43 cm; female >41 cm), and male sex. A score of 0–2, 3–4, and 5–8 indicated a low, intermediate, and high risk of OSA respectively.^[12]

All subjects underwent estimation of serum GH (glucose suppressed GH, baseline and after 1 h of oral intake of 75 g glucose), IGF-1, cortisol (8 am), follicle-stimulating hormone, prolactin, free thyroxine/total thyroxine (FT4/T4), thyroid-stimulating hormone, insulin, and intact parathyroid hormone by commercially available electrochemiluminescence assay. Besides, routine hematology and serum biochemistry for renal and liver functions, lipid profile, calcium, inorganic phosphorus, and albumin were carried out. Transthoracic echocardiography (two-dimensional-ECHO), pulmonary function tests (PFT), chest X-ray PA view, high-resolution computerized tomography (HRCT) of thorax, and overnight PSG were also performed.

Pulmonary function tests

Spirometry was performed as per the latest Indian guidelines on spirometry, using the ultrasonic transducer-based body plethysmography system (Power Cube Body with Diffusion; Ganshorn Medizin Electronic, Germany). Standard spirometric testing included maximal expiratory flow-volume loops (MEFs), VC, FEV1, peak expiratory flow (PEF), mean maximum expiratory flow when 25%–75% of FVC has been exhaled (MEF 25%–75%).

Body plethysmography was used to find specific airway resistance (sRAW), thoracic gas volume (TGV), total lung capacity (TLC), and residual volume (RV).

Polysomnography

Overnight PSG and continuous positive airway pressure (CPAP) titration (if indicated), was performed as per the latest American Academy of Sleep Medicine (AASM) guidelines,^[13] using an Alice 6 computerized polysomnogram system (32 channel Philips Alice 6 Respironics, Netherlands) at the designated sleep laboratory. Thirty-two channels were used to document: Sleep stages (four-channel electroencephalogram, electrooculogram, chin electromyogram, electrocardiogram channel, airflow at nose and mouth (nasal thermistor and cannulae), chest and abdominal respiratory movement (respiratory impedance), oxygen saturation (pulse oximetry), snoring (microphone) and body position. The PSG data were reviewed and manually validated at the laboratory by trained and experienced sleep specialists, and results were recorded for subsequent analyses. The sleep stages and respiratory events were scored according to the standard AASM Manual of Scoring of Sleep and Associated Events.^[13] Abnormal breathing events included apneas and hypopneas. Apnea was defined as the cessation of airflow $\geq 90\%$, as compared to baseline, for ≥ 10 s. Hypopnea was defined as either a reduction in airflow $\geq 30\%$ for ≥ 10 s accompanied by a $\geq 3\%$ desaturation or arousal, or a reduction in airflow $\geq 30\%$ for ≥ 10 s accompanied by a $\geq 4\%$ desaturation as compared to baseline. The apnea-hypopnea index (AHI) was the average number of apnea and hypopnea events per sleep hour. The events were further categorized into obstructive apneas (OAs) (cessation of airflow in the presence of respiratory effort), central apneas (CAs) (cessation of airflow with an absence of respiratory effort), mixed apneas (MAs) (a respiratory event during which a central apnea is followed by an obstructive component), and hypopnea. OSA was diagnosed when a patient had AHI ≥ 15 or if a patient with symptoms suggesting OSA had AHI ≥ 5 /h of total sleep time.^[14]

Radiological investigations

A chest X-ray (posteroanterior view) was taken in full inspiration. A non-contrast-enhanced HRCT of the thorax was performed on a 128 slice multi-dimensional CT scanner (Somatom Definition AS plus; Siemens Healthcare, Germany). The tube voltage was kept at 120 kV, and the tube current was 100–200 mAs depending on the patient's body habitus. High-resolution CT lung images were reconstructed with 0.6 mm slice thickness. The total radiation dose was approximately 7 mSv. Image analysis was done by a trained radiologist for the presence of any abnormality. Any additional neck or upper abdomen findings were also recorded. Anteroposterior and transverse diameters of the trachea at the level of the thoracic inlet were recorded. Quantitative analysis of inspiratory lung volume was done by tracing the lung margins on volume software (Syngo, Siemens). The total volume of the lung

was calculated using the threshold value of -500 to -1024 HU. For control subjects, tracheal diameter and lung volume were calculated from age-matched cases where CT chest was done as part of disease work-up.

Echocardiography

Doppler transthoracic ECHO was performed following a standard protocol, and echocardiograms were recorded. Color-Doppler ECHO measurements, transthoracic M-mode two-dimensional, and pulse Doppler were performed from standard parasternal views in the resting state in the left lateral position, as per the recommendations of the American Society of echocardiography.^[15] Several parameters were measured, including the inter-ventricular septum thickness, posterior wall thickness, left atrial dimension, left ventricular internal end-diastolic diameter, left ventricular systolic diameter, and left ventricular mass calculated by Devereux's Formula, modified with body surface area.

Statistical analysis

All the statistical analyses were performed using the SPSS statistical software, version 22.0 (SPSS Inc., Chicago, IL, USA). Demographic and clinical (continuous) variables have been presented with descriptive statistics (mean \pm standard deviation). Proportional data were expressed in terms of percentages. A $P < 0.05$ was considered a statistically significant value.

RESULTS

Demographic data, symptoms, and comorbidities [Table 1]

The mean age of acromegaly patients was 39.7 ± 13.2 years while mean age of healthy controls ($n = 34$) was 40.3 ± 13.0 years. The mean duration of symptoms of acromegaly was 5.43 ± 5.0 years (range 1–26 years). Sixty-five percent of patients had macro-adenoma at presentation. The mean serum IGF-1 and GH levels were 597.7 ± 357.8 $\mu\text{g/l}$ and 24.77 ± 54.42 ng/ml , respectively. Patients with acromegaly had significantly higher BMI (28.03 ± 5.71 kg/m^2) as compared to controls (24.08 ± 2.79 kg/m^2 ; $P < 0.05$); however, the mean height of both groups was similar. Respiratory symptoms in acromegaly subjects were exertional dyspnea (34%), frequent dry cough (37%), excessive daytime somnolence (43%), and fatigue (49%). Hypertension and diabetes mellitus were present in 26% and 40% of the acromegaly patients, respectively. The mean ESS score in acromegaly patients was 8.37 ± 4.12 (range 2–14), while the mean STOP-BANG score was found to be 3.60 ± 1.85 (range 0–7). Clinically significant ESS (>10) and STOP-BANG score (≥ 3) were present in 41% and 68.6% of acromegalics, respectively. STOP-BANG scoring in acromegaly patients, as compared to healthy controls, showed significantly higher number of subjects in intermediate and high OSA risk category [Table 1]. Neck circumference and pre-inspiration thoracic diameter were significantly higher in acromegaly subjects [Table 2].

Table 1: Clinico-demographic characteristics of acromegaly patients with controls

	Patients (n=35)	Controls (n=34)	P
Age (years)	39.77±13.22	40.32±13.04	NS
Weight (kg)	72.69±17.33	62.29±9.39	<0.05
Height (cm)	160.37±7.03	160.41±7.68	NS
BMI (kg/m ²)	28.03±5.71	24.08±2.79	<0.05
Epworth Sleepiness Score (ESS)			
Normal (≤10)	21 (60.0%)	22 (64.7%)	NS
Mild Excessive (11-12)	9 (25.7%)	7 (20.6%)	NS
Moderate Excessive (13-15)	3 (8.6%)	4 (11.8%)	NS
Severe Excessive (16-24)	2 (5.7%)	1 (2.9%)	NS
STOP-BANG Score			
Low OSA Risk (0-2)	11 (31.4%)	17 (50.0%)	<0.05
Intermediate OSA Risk (3-4)	9 (25.7%)	12 (35.3%)	<0.05
High OSA Risk (5-8)	15 (42.9%)	5 (14.7%)	<0.05

Expressed as number (percentage) or mean±standard Deviation; P value: NS: Non-significant. (BMI: Body mass index, OSA: Obstructive Sleep Apnea)

Pulmonary function tests

Spirometry was classified as a normal or suggestive of either restrictive or obstructive pattern. Acromegalics had significantly higher prevalence of abnormal spirometry patterns, with the restrictive pattern and obstructive pattern seen in 45.7% and 11.4% respectively (control subjects: Restrictive 5.9%, obstructive 17.6%, *P* < 0.05) [Table 2]. On body-plethysmography (measurement of static lung volumes), the percent predicted values for TLC, TGV, and RV were also significantly higher in acromegaly patients. However, there were no significant differences in the mean FVC, FEV1, MEF (25%–75%), and sRAW values [Table 2].

Polysomnography [Table 2]

Acromegaly patients had a significantly higher prevalence of OSA (acromegaly 71.4% vs. control 38.2%; *P* < 0.05), and higher mean AHI (acromegaly 16.91 ± 18.00 vs. control 7.86 ± 7.84; *P* < 0.05). AHI in acromegalic

Table 2: Pulmonary evaluation and polysomnographic findings in acromegaly patients vs. controls

	Patients (n=35)	Controls (n=34)	P
Neck Circumference (cm)	40±2.55	36.8±5.6	<0.05
Thoracic Dimensions (cm)			
Pre-Inspiration AP	112.41±6.45	109.3±6.5	0.05
Post-Inspiration AP	106.55±5.60	103.5±5.6	<0.05
Pre-Inspiration Lateral	32.64±6.32	29.2±6.3	<0.05
Post-Inspiration Lateral	29.2±5.6	25.9±5.7	<0.05
Spirometry Patterns			
Normal	15 (42.9%)	26 (76.5%)	<0.05
Restriction	16 (45.7%)	2 (5.9%)	<0.05
Obstruction	4 (11.4%)	6 (17.6%)	<0.05
Pulmonary Function Test Values			
FEV1(% predicted)	2.34±1.12	2.08±0.65	NS
MEF25-75 (% predicted)	2.63±1.10	2.34±0.95	NS
sRAW (% predicted)	109.69±14.93	114.23±8.38	NS
TGV (% predicted)	107.51±14.05	98.93±12.29	<0.05
TLC (% predicted)	111.24±11.19	99.67±17.71	<0.05
RV (% predicted)	106.59±8.44	98.24±14.77	<0.05
Polysomnographic Findings			
Total recording time (minutes)	442.89±118.54	414.98±84.96	NS
Total sleep time (minutes)	319.94±147.10	330.43±71.42	NS
Sleep Efficiency (%)	80.83±6.16	79.57±4.05	NS
Sleep Latency (minutes)	16.92±7.06	16.84±9.36	NS
Non-REM Sleep (%)			
N1 (%)	12.69±3.84	13.50±4.68	NS
N2 (%)	45.07±12.36	42.79±8.52	NS
N3 (%)	25.22±11.95	26.67±9.68	NS
REM Sleep (%)	17.02±7.18	17.03±7.11	NS
Total number of central apnea events	24.63±37.82	3.21±5.50	<0.05
Total number of mixed apnea events	11.00±19.46	3.50±5.96	<0.05
Total number of obstructive apnea events	34.86±44.37	9.71±10.48	<0.05
Total number of obstructive hypopnea events	26.80±48.55	9.88±6.73	<0.05
AHI (per hour)	16.91±18.00	7.86±7.84	<0.05
Time spent with saturation below 90% (min)	41.80±84.69	15.97±16.53	0.085
Obstructive Sleep Apnea (OSA)			
Normal	10 (28.6%)	16 (47.1%)	<0.05
Mild OSA	11 (31.4%)	15 (44.1%)	<0.05
Moderate OSA	7 (20.0%)	1 (2.9%)	<0.05
Severe OSA	7 (20.0%)	2 (5.9%)	<0.05
Total OSA	25 (71.4%)	18 (38.2%)	<0.05
Titration Required	13 (37.1%)	3 (8.8%)	<0.05
CPAP Prescribed	7 (20.0%)	1 (2.9%)	<0.05
HRCT Thorax Findings			
Tracheal diameter AP (mm)	17.89±2.21	16.47±2.88	<0.05
Tracheal diameter Transverse (mm)	16.17±2.61	15.87±2.09	NS
Total CT Lung Volume (ml)	3710.34±1253.41	3049.12±886.30	<0.05

Table 3: Comparison of patients of Acromegaly with and without OSAS

	OSAS (n=25)	Non-OSAS (n=10)	P
Age (years)	41.4±13.4	33.6±12.4	NS
Sex (M: F)	1.3:1	1:2.4	NS
Neck circumference (cm)	40.9±3.3	40.1±2.1	NS
BMI (kg/m ²)	28.3±5.5	26.3±6.6	NS
Epworth sleepiness score (ESS)	7.9±3.7	9.5±5.1	NS
STOP-BANG score	3.8±1.9	3.0±1.7	NS
Serum Glucose (Fasting) (mg/dl)	104.3±10.6	110.9±36.6	NS
Serum Insulin (mIU/L)	7.1±8.3	18.6±39.20	NS
Serum IGF-1 (ug/L)	516.6±415.97	571.1±283.4	NS
Serum GH (ug/L)	22.12±52.04	10.95±14.07	NS
Serum Free-T4 (pmol/L)	104±27.2	103±11.8	NS
Serum TSH (mIU/L)	1.27±1.57	1.83±1.18	NS
Left Ventricular Mass (grams)	206.7±56.1	200.6±74.3	NS
Post Wall Thickness (mm)	13.5±5.8	12.9±7.0	NS
Inter Ventricular Thickness (mm)	13.4±5.8	12.9±6.9	NS
Left ventricular Mass Index (g/m ²)	114.3±32.1	115.7±33.4	NS

Expressed as Mean±Standard Deviation, P NS: Non-significant. (BMI: Body mass index, IGF-1: Insulin-like growth factor-1, GH: Growth Hormone, T4: Thyroxine, TSH: Thyroid-stimulating hormone)

Table 4: Echocardiography findings between cases and controls

	Patients (n=35)	Controls (n=34)	P
Left Ventricular Mass (grams)	204.96±60.72	173.99±31.72	<0.05
Posterior Wall Thickness (mm)	13.34±6.06	10.59±1.28	<0.05
Inter Ventricular Thickness (mm)	13.31±6.06	10.59±1.26	<0.05
Left ventricular Mass Index (g/m ²)	114.32±32.66	104.70±17.07	NS

subjects were normal (<5), mild (5–14), moderate (15–29) and severe (≥30) in 28.6%, 31.4%, 20%, and 20% of subjects, respectively. There were significantly higher ($P < 0.05$) number of sleep-related respiratory events in the acromegaly patients, i. e., central apnea events (acromegaly 24.62 ± 37.82 vs. control 3.21 ± 5.5), mixed apnea events (acromegaly 11 ± 19.46 vs. control 3.50 ± 5.96), and obstructive apnea events (acromegaly 34.86 ± 44.37 vs. control 9.71 ± 10.48). The acromegaly patients (37.1%) with moderate to severe OSA required CPAP titration study and were thereafter recommended the use of domiciliary nocturnal CPAP therapy. The AHI value in acromegaly patients, however, showed no correlation with the serum IGF-1 levels, BMI, and duration of the disease. Comparison of acromegaly patients with OSA ($n = 25$) with those without OSA ($n = 10$) showed no significant differences in age, sex, neck circumference, BMI, serum GH and IGF-1, and ECHO findings [Table 3].

Radiological observations

The chest X-ray was found to be normal in 74% of the acromegaly patients. The common radiological abnormalities on chest X-ray were abnormalities of the diaphragm ($n = 3$, raised right diaphragm 1, left raised diaphragm 1, right diaphragmatic hump 1), calcified granuloma right lung ($n = 1$), fibrotic opacity in the left middle zone ($n = 1$), unfolding of the aorta ($n = 1$), cardiomegaly ($n = 2$), right lower lobe opacity ($n = 1$), and widened mediastinum ($n = 1$). HRCT thorax findings

were normal ($n = 22$), tubular bronchiectasis ($n = 6$), fibrotic patch ($n = 4$), atelectasis ($n = 3$), calcified granuloma ($n = 3$), calcified lymph nodes ($n = 2$), and residual thymic tissue ($n = 2$). The tracheal AP diameter and total lung volume were significantly higher in acromegaly as compared to controls [Table 2].

Echocardiography

ECHO was normal in 60.3% of the acromegaly patients while diastolic dysfunction and systolic dysfunction were seen in 29.8% and 9.9% of acromegalic subjects, respectively. Acromegalic subjects had higher LV mass, posterior wall thickness and inter-ventricular thickness as compared to control subjects while the LV mass index was similar [Table 4].

DISCUSSION

Respiratory comorbidities, such as SA, in particular obstructive variant, poor sleep quality, abnormal respiratory drive, respiratory muscle dystrophia, increased lung volumes, reduced diffusion capacity, decreased lung recoil, small airway dysfunction, craniofacial deformity, rib cage deformity, vertebral fractures, and kyphoscoliosis are common in acromegaly.^[1] It has been estimated that up to 60% of acromegalic patients die from cardiovascular disease, 25% from respiratory disease, and 15% from malignancies.^[16] The prevalence of SAS in active acromegaly ranges from 40% to 80% in various studies, depending on the diagnostic criteria.^[3,4] We observed clinically diagnosed SA in 74% of active acromegaly subjects and the prevalence is concordant with previous studies. Interestingly, we also observed SA in 24% of the age- and sex-matched non-acromegalic subjects in Caucasians. Various global epidemiologic studies have demonstrated the prevalence of OSA in general population between 6.5%–17.5% in women and 15%–35% in men.^[17] In India, Udawadia *et al.*^[18] have reported OSA prevalence of 7.5% in urban men. OSA is more common in males than females in general population,^[19] however, the prevalence is similar in males and females in our subjects with acromegaly.

Based on the diagnostic criteria, three types of SAS are recognized in acromegalics: A central type, characterized by absent or reduced activity of the respiratory center; an obstructive type, characterized by intermittent obstruction of the upper airways with preservation of thoracic and abdominal respiratory movements; and a mixed type. The second type of SAS is the prevailing form in acromegaly seen in up to 70% of these patients.^[5] OSA in acromegalics has been attributed to IGF-1 induced changes of soft, cartilaginous, and bony tissues at the level of craniofacial, pharyngeal, and laryngeal structures which hamper the airflow through the upper airways during sleep. Various studies have reported macroglossia, swelling/lengthening of the soft palate, impaired airflow transit, swelling/inspiratory collapse of the pharyngeal walls, thickening of true and false vocal cords, overgrowth of mandible, maxilla

and hyoid bones, prognathism, and goiter.^[6] In our study, 71.4% of acromegalics had OSA with a mean AHI of 16.9/h. Significantly, 40% of these acromegalics with OSA had moderate to severe disease. We observed dyspnea in 34%, cough 37%, excessive daytime somnolence in 43%, and fatigue in 49% of our subjects. Weiss *et al.* reported snoring in 78%, fragmented sleep in 60%, daytime somnolence in 51%, and morning sleepiness and morning headache in 16% of cases.^[20]

We also observed central and mixed apnea events in a significant proportion of our acromegaly subjects. The pathogenesis of central apnea in acromegalics is still speculative. Studies have shown that central apnoea has significantly higher random GH, 24-hrs GH, and IGF-1 levels.^[21] High GH/IGF-1 levels possibly have a direct effect on the breathing center or through an enhanced somatostatin tone^[22] and decrease chemosensitivity to hypoxia in humans.^[23]

It is still debatable whether the severity of OSA is associated with disease activity or disease duration or both.^[4,24] We were unable to demonstrate any such correlation. However, some of the previous studies have shown a decline in SA after curative treatment of acromegaly, either through surgery or medical management.^[25,26] Although partial reversibility may be observed once the biochemical control is achieved and lowering GH/IGF-1 is rapidly followed by interstitial fluid excretion resulting in an approximately 9% weight loss and a reduction of soft tissue thickness which improves SA severity, but up to 40% of those with controlled acromegaly have persistent SA, and initiation or titration of positive airway pressure treatment may be necessary.^[6,27] The effect of medical management with somatostatin analogue (SSA) may be more profound on central SA. A significant decrease in the apnoeic episodes, particularly in the central form of SA, has been documented after a 6-month treatment with octreotide.^[28] The beneficial effects of treatment with octreotide in SA have been reported, but changes to the bones and cartilaginous structures in the respiratory tract are still largely deemed permanent.

There are only few studies on lung functions in acromegaly. Almost 60% of acromegalics in this study were having lung function abnormality. There is also a documented increase in lung volumes, which was demonstrated both by body plethysmography and HRCT. The values of TGV, TLC, and RV in acromegaly subjects in our study are significantly higher than the age- and sex-matched controls. Early studies have reported a significant increase of lung volume (pneumonomegaly) due to an increase in the number rather than in the volume of the alveoli in up to 50% of patients, envisaging a proliferative and differentiative phenomenon.^[29-31] As a result, an increase in lung capacity by 81% in male and 56% in female patients had been reported. In another study of 109 patients, acromegalics had greater lung volume as measured by maximal VC, intra-TGV, TLC, and RV.^[32] In 40.4% of the patients, the increase in RV was clinically

relevant (i.e. more than 120% of predicted value), but the duration of disease did not correlate with lung function abnormalities. In addition, hypertrophy of interstitial tissue, as well as air trapping, have also been observed.^[32]

The previous studies have also suggested lung function changes hinting at airway obstruction in acromegalics, with a significantly smaller PEF noted in acromegaly patients, in addition to reduced maximum expiratory flow when 75% of the FVC has been exhaled (MEF75%). The latter indicates small airway disease in acromegaly patients. A clinically relevant reduction (i.e. <80% of predicted value) in MEF75% was found in 56.5% of patients. However, total specific resistance (sRtot) was reduced, and forced expiratory volume in 1 s (FEV1) was elevated. 55 In our study, the obstructive pattern on spirometry was seen only in 11.4% of patients. Also, there was no difference between the FEV1, sRAW, and MEF25%–75% values of acromegalics as compared to controls. Despite the findings in our study, it is however postulated that GH-induced proliferation of interstitial tissue, pneumocytes, smooth muscle cells, and vascular epithelium cause increased thickness or tortuosity of the bronchial wall, increased lung volumes, or vascular congestion, or a combination of these. This further leads to decreased elasticity of the lung and eventually results in obstruction of the small airways.^[2] Prior studies looking into lung functions in acromegaly have shown inconclusive findings on the association between disease activity and lung functions. Further studies are required to explore whether long-term application of SSA in acromegaly improves lung functions through primary effect on lung tissue and airways.

Few studies have also described HRCT thorax findings in acromegaly. Camilo *et al.*, had described the presence of air trapping, airway calcification, and bronchiectasis in 60%, 40%, and 35% of cases of acromegaly, respectively.^[33] An increase in lung mass by almost 25% with a large amount of nonaerated and poorly aerated compartments had also been reported.^[34] In our study, bronchiectatic changes were noted in 17% of cases, mostly tubular affecting few lobes. Mosaic attenuation, limited to few segments, was noted in 11.4% of cases, most likely due to small airway involvement. We also observed an increase in anteroposterior tracheal diameter and total lung volume.

Cardiovascular complications are frequently encountered in patients with acromegaly as a result of hypersecretion of GH causing endothelial dysfunction, increased vascular intima-media thickness, increased size of cardiac myocytes, myocardial interstitial fibrosis, left ventricular hypertrophy even in normotensive subjects, and with subjects with short duration of disease.^[1,2] Patients also have left ventricular diastolic dysfunction, reduced exercise tolerance, left ventricular failure, accelerated atherosclerosis, complex ventricular arrhythmia, and increased cardiovascular mortality. We observed hypertension in 26% of patients. ECHO demonstrated diastolic and systolic dysfunction in 28.7% and 8.7% of patients, respectively.

This study highlights the high prevalence of SA, both central and obstructive, in Indian patients with active acromegaly. Increased lung volumes were seen both by body plethysmography and HRCT thorax. In addition, these patients had diastolic and systolic dysfunction on ECHO. Therefore, all the patients with active acromegaly should be encouraged to undergo PSG, PFT, and ECHO studies as part of a comprehensive evaluation of the disease and associated comorbidities.

Financial support and sponsorship

This work was supported by The Council of Science and Technology, Uttar Pradesh (UPCST), India. (Project Grant No. UPCST/SERPD/D-117).

Conflicts of interest

There are no conflicts of interest.

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