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Early Lung Function Abnormalities in Acromegaly

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Abstract

Background Acromegaly is an insidious disorder caused by a pituitary growth hormone (GH)-secreting adenoma resulting in high circulating levels of GH and insulin-like growth factor I (IGF-I). Respiratory disorders are common complications in acromegaly, and can severely impact on quality of life, eventually affecting mortality.

Objectives The present study aimed to explore structural and functional lung alterations of acromegalic subjects.

Methods We enrolled 10 consecutive patients (M/F: 5/5) affected by acromegaly. In all patients, magnetic resonance imaging (MRI) revealed the presence of pituitary tumor. All patients underwent clinical, lung functional, biological, and radiological assessments. Ten healthy age-matched subjects also served as controls.

Results No statistically significant differences in lung function were detected between acromegalic and healthy subjects ($p \geq 0.05$ for all analyses). However, the diffusing capacity for CO (TLCO) was significantly lower in the acromegalic group than in healthy subjects (TLCO% predicted: 78.1 ± 16 vs. 90 ± 6 %, respectively, $p = 0.04$; KCO% predicted: 77 ± 16 vs. 93 ± 5 %, $p = 0.02$, respectively). None of the lung function parameters correlated with duration of the disease, or with inflammatory marker of the airways. In acromegalics, biological (exhaled NO concentrations) and imaging (total lung volume, TLV, and mean lung density, MLD) evaluations were within normal values. The TLV measured by HRCT was 3540 ± 1555 ml in acromegalics, and the MLD was −711 ± 73 HU. None of the lung functional, radiological, and biological findings correlated with GH or IGF-I levels, and no correlation was found with duration of disease.

Conclusions In the current study, lung function evaluation allowed to detect early involvement of lung parenchyma, as assessed by TLCO and KCO, even in the absence of parenchymal density alterations of the lung by HRCT. These findings suggest to routinely include the carbon monoxide diffusing capacity in the lung function assessment for an early intervention in acromegaly.

Keywords Imaging · Lung function · Acromegaly · Diffusing capacity

Abbreviations

COPD	Chronic obstructive pulmonary disease
FENO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the 1st second
FVC	Forced vital capacity
GH	Growth hormone
HRCT	High-resolution computed tomography
HU	Hounsfield unit
IGF-I	Insulin-like growth factor I
KCO	Carbon monoxide transfer coefficient
LAV	Low attenuation volume
MRI	Magnetic resonance imaging
OGTT	Oral glucose tolerance test

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SAS Sleep apnea syndrome
TLC Total lung capacity
TLCO Transfer factor of the lung for carbon monoxide

Introduction

Acromegaly is an insidious disorder caused by a pituitary growth hormone (GH)-secreting adenoma resulting in high circulating levels of GH and insulin-like growth factor (IGF-I) [1]. During the natural course of acromegaly, the elevated GH and IGF-I levels lead to a wide range of cardiovascular, respiratory, endocrine, and metabolic comorbidities that contribute to significantly enhanced mortality. The goals of therapy in patients with acromegaly are the elimination of morbidities associated with the disease and normalization of the increased mortality. Surgery, radiation, and medical treatments are available for lowering GH and IGF-I hypersecretion, controlling pituitary tumor mass effects, and improving morbidity, although no single therapy is comprehensively successful in controlling the disease and its clinical manifestations, and often multimodal therapies are required for disease control through suppression of GH hypersecretion, reduction of IGF-I levels, and control of tumor growth [2, 3]. Comorbidities should be evaluated and treated during acromegaly within the clinical context, and the reduction in GH and IGF-I levels is a valuable and accurate marker for improvement of the comorbidity associated with acromegaly [4].

Respiratory disorders are common complications in acromegaly, and the mortality rates from respiratory causes are threefold more common than in the general population [5]. Deformities of facial bones, edema, and hypertrophy of the mucosae and pharyngeal and laryngeal cartilages, enlargement of the tongue and inspiratory collapse of the hypopharinx, may contribute to respiratory alterations. Generalized soft-tissue thickening is a well-known feature of acromegaly and is related to glycosaminoglycan deposition, as well as to increased collagen production by connective tissue and tissue edema. The sleep apnea syndrome (SAS) is the most common respiratory alteration in acromegalic individuals, affecting 60–70 % of acromegalic patients and may present as obstructive, central, or mixed [6]. In addition, acromegalic pneumomegaly is frequently observed and, as suggested by lung functional studies, it might be due to an increased number, rather than volume, of the alveoli, although data are controversial [7, 8]. Despite the increase in lung size, however, the single-breath carbon monoxide transfer coefficient (KCO) appears to be lower than expected, thus implying parenchymal alterations.

In the attempt to establish whether, and to what extent, the lung is involved in acromegaly, the present study aimed to explore structural and functional lung alterations of acromegalic subjects. To this aim, clinical, radiological, biological, and lung functional assessments were performed.

Material and Methods

Subjects

For the purpose of the study, we enrolled ten consecutive patients (M/F: 5/5) affected by acromegaly visiting the Endocrinology Section of the University of Palermo in 2011. Smoker patients or those with already known respiratory diseases were excluded from this study. Ten healthy age-matched subjects served as controls. They had never experienced respiratory symptoms consistent with the diagnosis of chronic obstructive pulmonary disease (COPD) or other lung disease, nor had they ever been diagnosed with COPD or another lung disease by a physician, and none of them was on any respiratory medication regimen. Out of the ten patients included in the study, three were newly diagnosed patients, not receiving any acromegalic treatment, three were treated with first-line octreotide-long acting release (20–30 mg every 28 days), 1 with lanreotide autogel (90 mg every 28 days), 2 with pegvisomant (10–15 mg/daily), and one patient had recently received pituitary surgery. In all patients, MRI (magnetic resonance imaging) scan revealed the presence of a pituitary tumor. The mean duration of disease was established by patient interview, patients' pictures, and onset of osteoarticular symptoms.

Based on the nadir GH after oral glucose tolerance test (OGTT) and IGF-1 levels, patients were divided into those with controlled ($No = 5$) and those with uncontrolled ($No = 5$) acromegaly. Cut-off level for controlled subjects was 1 μg/l for random GH and 0.4 μg/l after OGTT, together with IGF-1 in the age-adjusted normal range, with the exception of patients under pegvisomant treatment, in whom only IGF-1 levels were considered as parameter of activity of disease [9]. At the time of hospitalization, all patients signed an informed consent for the scientific use of their data. The study was approved by the Institutional Review Board of the Faculty of Medicine, University of Palermo, given that the identity of the participants remained anonymous during database analysis.

Study Design

The study included a total of three visits. All enrolled patients underwent an initial assessment (Visit 1) in which

body mass index, and systolic and diastolic blood pressures were measured in the morning. After an overnight fast, mean fasting plasma GH (at least three blood samples at 30-min intervals) and IGF-I levels were measured. OGTT was performed in all patients by measuring plasma blood glucose, insulin levels, and GH every 30 min for 2 h after 75 g oral glucose load. The pulmonary evaluation was conducted on two days. The first day (Visit 2) included clinical, biological, and lung function assessments. On a separate occasion (Visit 3), lung imaging procedures were carried out. All patients were in stable conditions on study days.

Clinical and Functional Assessments

Functional assessment included measures of static and dynamic lung volumes, as well as single-breath diffusing capacity for CO, which were performed using a fully computerized water-sealed Stead-Wells spirometer (Baires System; Biomedin; Padua, Italy). The transfer factor of the lung for CO (TLCO) and the KCO was measured to evaluate the extent of lung parenchymal destruction. At least two determinations of TLCO that were within 5 % of each other were obtained, and the highest value was retained for analysis. Measurements were made in accordance with the European Thoracic Society standardisation document on lung volume measurements [10]. FEV_1% (forced expiratory volume in the 1st second) predicted and FVC% (forced vital capacity) predicted, as well as TLC% (total lung capacity) predicted, TLCO% predicted, and KCO% predicted were calculated and used for the analysis.

Biological Assessment

Exhaled nitric oxide (FENO) was measured with a standardized single-breath method using the electrochemical analyzer (Hypair FENO®, Medisoft), which was calibrated daily. The measurement procedure was consistent with guidelines published by the American Thoracic Society/European Respiratory Society [11]. Subjects were in sitting position during the entire procedure. Each individual was asked to take a deep inspiration from room air and, immediately after, to forcefully exhale through the mouthpiece that was connected to the on-line analyzer. To determine if subjects maintained a constant flow-rate during exhalation, a continuous monitoring of expiratory flow-rate by graphic display on the monitor screen was used. All samples were acquired in the morning between 11:00 and 12:00. FENO was obtained as the mean of three acceptable measurements at the airflow rate of 50 ml/s.

Imaging Assessment

Each subject underwent high-resolution computerized tomography (HRCT), which was performed by spiral computed tomography (multidetector 64 channels equipment, Philips Medical System, Cleveland, OH), with a setting of 120 kVp, 200 mAs, a 0.9-mm slice thickness, a rotation time 0.5 s, and a reconstruction interval of 0.45 mm, pitch 0.923, during a single breath and moved caudally. Images were reconstructed at a window level of—600 Hounsfield units (HU) and a window width of 1600 HU.

Two radiologists (MB and FC) evaluated the CT scans independently, excluding any radiological abnormality of the lung parenchyma. Total lung volume and parenchymal density on the HRCT scans as an estimate of parenchymal damage were measured at full inspiration. Total lung volume was calculated and expressed in cm^3. Parenchymal density was expressed by lung attenuation parameters, such as mean lung density at FRC, functional residual capacity (Mean HU_{exp}) and at TLC, total lung capacity (Mean HU_{insp}); in addition, the percent of the lung with a low attenuation volume at TLC (i.e., below −950 HU, LAV) was measured as an estimate of the degree of emphysema.

Statistical Analysis

Statistical analysis was performed using Statview® 5.0 (SAS Institute Inc., Cary, NC, USA). Univariate analysis and correlation analysis were performed. Data are expressed as mean ± SD. Significance level was set at $p \leq 0.05$.

Results

The clinical characteristics and endocrine status of the study subjects are presented in Table 1. Duration of the disease was 5.5 ± 3.9 yrs (range: 1–11 years). FEV_1% predicted was 115 ± 21 % (mean ± SD, range: 89–156 %), FVC % predicted was 120 ± 21 % (range: 91–162 %), FEV_1/FVC was 0.79 ± 0.5 (range: 0.73–0.89), and TLC predicted was 110 ± 16 % (range: 93–144 %); in addition, TLCO% predicted was 78.1 ± 16 % (range: 58–111 %) and KCO% predicted equal to 77 ± 16 % (range: 56–92 %). Finally, FeNO was 12 ± 8 ppb (range: 4–30 ppb). Healthy controls were matched by gender (5 males and 5 females for each group), age (44 ± 13 vs. 52 ± 10 years, $p = 0.17$), and height (168 ± 9 vs. 169 ± 10 cm, $p = 0.85$). In healthy controls, FEV_1% predicted was 110 ± 7 % (mean ± SD, range: 99–122 %), FVC % predicted was 112 ± 7 % (range: 100–123 %), FEV_1/FVC was 0.82 ± 1.3 (range: 0.80–0.84), and TLC predicted was 105 ± 10 % (range: 90–117 %). TLCO%

Table 1 Demographic and clinical characteristics of acromegalic subjects

Patient No.	Gender	Age	Smoking	BMI	Duration of disease (yearr)	GH mean baseline (μg/L)	GH after oral glucose load (μg/L)	Mean IGF-1 (μg/L)	Concomitant Diseases	GH hypersecretion treatment
1	M	65	F	31.1	10	6.8	3.7	756	Hypertension, dyslipidemia	Octreotide LAR 20 mg/monthly
2	M	46	N	26.7	1	8	###	848	Hypertension	None (newly diagnosed)
3	F	53	N	37.2	1	3	1	600	Hypertension	None (newly diagnosed)
4	M	57	N	34.6	5	3.28	###	231	Hypertension, dyslipidemia	Post-surgery
5	F	50	N	26	4	###	###	722	Hypertension	Octreotide 30 mg/monthly, pegvisomant 15 mg/daily, cabergoline 1 mg/weekly
6	F	39	N	29.4	6	1.24	0.56	115	Hypothyroidism	Lanreotide 90 mg/2 month
7	M	52	N	24.8	11	###	###	137	None	Octreotide 30 mg/monthly, pegvisomant 10 mg/daily
8	M	41	N	30.5	1	31	26	1049	None	None (newly diagnosed)
9	F	48	N	39.4	6	1.6	0.8	273	Hypertension, dyslipidemia.	Octreotide 30 mg/monthly
10	F	71	N	29	10	1.2	0.8	225	Hypertension, dyslipidemia	Octreotide 20 mg/monthly

predicted and KCO% predicted were 90 ± 6 % (range: 80–100 %) and 93 ± 5 % (range: 85–101 %), respectively. We did not find statistically significant differences in lung function between acromegalic and healthy subjects ($p \geq 0.05$ for all analyses). However, TLCO was significantly lower in the acromegalic group than in healthy subjects (TLCO% predicted and KCO% predicted: $p = 0.04$ and $p = 0.02$, respectively). Complete lung function characteristics of acromegalic and control subjects are presented in Table 2 and 3, respectively.

When we divided the patients according to the disease activity, no differences in static and dynamic lung volumes, as well as diffusing CO capacity, were detected between patients with controlled and uncontrolled acromegaly ($p > 0.05$ in all comparisons). In addition, none of the lung function parameters correlated with duration of the disease.

In acromegalic subjects, the total lung volume measured by HRCT was 3540 ± 1555 ml, the mean lung density was −711 ± 73 HU, and LAV% total was 6.6 ± 6 %. None of the imaging parameters differentiated acromegalic from healthy subjects, or between active and inactive disease. However, the lung density evaluated by HRCT significantly correlated with TLCO% predicted ($r = 0.70$, $p = 0.03$).

Additional investigations were performed in acromegalic subjects with the aim to evaluate which factors can eventually influence the carbon monoxide transfer coefficient and the diffusing capacity for CO. The alternative hypothesis that pulmonary hypertension can affect the current findings was ruled out by normal values obtained with transthoracic echocardiography. In addition, nocturnal oxygen monitoring was performed to screen for nocturnal reduction in oxygen saturation. All but one subject showed during the recording time an oxygen saturation higher than 90 % (mean value: 94 %).

Discussion

Acromegaly is considered a rare disease in the general population. However, its impact on morbidity and mortality, as well as on health service costs, is not trivial. Respiratory disorders are common complications in acromegaly, and can severely impact on quality of life, eventually affecting mortality. Thus, early identification of lung function impairment could contribute to proper management of the disease. In the current study, lung function evaluation allowed to detect early involvement of lung parenchyma, as assessed by TLCO and KCO, even in the absence of parenchymal density alterations of the lung by HRCT.

Studies investigating the involvement of the respiratory system in acromegaly have primarily focused on the occurrence of obstructive sleep apnea, which is a common disorder in this disease [6]. Other lung abnormalities, such as larger lungs, were described by Siafakas and colleagues [12]. Trotman-Dickenson and colleagues [13] assessed pulmonary function and disease activity in patients with acromegaly (19 men and 16 women): large lungs occurred

Table 2 Lung function in acromegalic patients

Patient No.	FCV (%)	VC (%)	FEV1 (%)	FEV1/FVC	RV (%)	FRC (%)	TLC (%)	RV/TLC (%)	TLCO (%)	KCO (%)	FeNo (ppb)
1	110	106	114	81	92	81	98	90	87	88	23
2	98	94	89	74	102	88	95	104	83	92	8
3	140	142	142	85	110	92	122	92	87	91	6
4	91	88	102	89	109	107	93	113	72	89	12
5	127	127	114	77	122	116	120	98	111	90	5
6	122	122	114	80	111	96	116	94	66	62	4
7	162	155	156	78	131	161	144	86	71	56	5
8	128	125	124	77	112	94	119	84	62	58	12
9	111	112	102	78	89	78	100	90	84	87	16
10	108	110	96	73	101	94	97	102	58	56	30
Mean ± SD	119.7 ± 20.8	118 ± 21	115 ± 20.7	79.2 ± 4.8	107.9 ± 12.7	100.7 ± 24	110 ± 16.4	95.3 ± 8.9	78.1 ± 16	77 ± 16	12 ± 8.2

Table 3 Lung function in healthy subjects

Patient No.	Gender	Smoking	Age	FCV (%)	VC (%)	FEV1 (%)	FEV1/FVC	RV (%)	FRC (%)	TLC (%)	RV/TLC (%)	TLCO (%)	KCO (%)
1	F	N	42	100	106	99	81	100	88	102	97	80	87
2	F	N	64	105	105	99	80	83	85	90	91	88	90
3	F	N	33	115	116	108	81	120	113	117	103	100	101
4	F	N	28	123	124	114	81	109	121	120	90	97	99
5	F	N	60	115	116	112	82	111	119	107	101	92	93
6	M	N	47	120	114	120	81	127	139	116	99	85	86
7	M	N	63	119	114	122	80	119	117	112	95	97	98
8	M	N	35	108	104	111	84	70	92	94	71	82	85
9	M	N	43	106	102	106	83	94	76	99	92	92	95
10	M	N	29	110	105	110	83	93	94	95	95	91	94
Mean ± SD			44 ± 13.1	112.1 ± 7.1	110.6 ± 6.8	110.1 ± 7.2	81.6 ± 1.3	102.6 ± 17	104 ± 19	105.2 ± 10.2	93.4 ± 8.5	90.4 ± 6.3	92.8 ± 5.4

in 12 patients (34 %) and upper airflow obstruction in 17 patients (50 %). More recently, studies have focused on structural and functional abnormalities of the lung that may be linked to the acromegalic-related pathological processes. In this respect, a cross-sectional study including 20 acromegalic patients and 20 age-and height-matched control subjects was conducted with the objective to describe the abnormalities in lung structure and function [14]. The main findings in HRCT in acromegalic patients were air trapping, airway calcification, and bronchiectasis, which were observed in 60, 40, and 35 % of cases, respectively. As in our study, there was no significant correlation between the levels of GH and insulin-like growth factor I (IGF-I) and lung function. Interestingly, the diffusing capacity for CO in the two studies was within the normal range, and not different from healthy subjects. These observations are in contrast with our findings. As discussed below, we reasonably excluded parenchymal causes. We believe that the discrepancy between our and other studies is only apparent, since the latter showed larger lung volumes than healthy controls, perhaps explaining normal TLCO values. This is further confirmed by the fact that our study subjects did not differ in terms of height. Other authors hypothesized that the diffusing capacity is reduced both in normal and acromegalic subjects with large lungs [15, 16], as extrapolated by findings of reduced values associated with increasing height in healthy children, suggesting greater recruitment of pulmonary vascular bed at the apexes in the shorter subjects.

It has been accepted that the excess of GH in acromegaly induces growth of the lungs. However, the mechanism by which increased lung growth occurs in acromegaly is not clear, because studies gave contradictory results. In a study on the possible mechanisms for the increased lung growth in acromegalic subjects, Brody et al. [8] found increased values for TLC, normal elastic recoil, and normal specific lung compliance. The authors found normal values for TLCO and a reduced KCO, which suggested that the increased size of the lung in acromegaly resulted from an increase in alveolar size rather than number, resulting from an alteration of the elastic properties of the lungs. Alternative hypotheses, such as the contribution of pulmonary hypertension and the occurrence of nocturnal reductions in oxygen saturation, were reasonably excluded in the current study. Since the reduced carbon monoxide transfer coefficient and the reduced diffusing capacity cannot be justified by parenchymal density alterations of the lung by HRCT, we suggest the occurrence of an alveolar membrane damage or a microvascular damage in acromegalic subjects. Further studies are needed to test this hypothesis.

A significant correlation between duration of acromegaly and lung size was previously demonstrated [17]. It has been suggested that when duration of disease exceeds eight years, patients are very likely to develop abnormalities of lung function either primarily from the effects of acromegaly on the lung, or due to the associated cardiovascular and thoracic skeletal abnormalities. Moreover, some studies showed that a decrease in lung size occurs in patients who develop GH deficiency and thus, that normal levels of GH are necessary for maintaining normal lung size during adult life. De Troyer et al. [18] investigated the pulmonary function in eight patients with hypopituitarism in order to determine if the lung is affected by the generalized visceral atrophy of hypopituitarism; six patients with acromegaly and trophic hormone deficiencies were studied for comparison. The patients with hypopituitarism, including one with isolated GH deficiency, had a restrictive type of ventilatory impairment, which could not be related to neuromuscular impairment or to an abnormality of chest wall mechanics. Donnelly and colleagues [7] hypothesized that lung size in acromegaly is achieved through a process of alveolar hyperplasia rather than hypertrophy. They attributed the decrease in KCO due to an increase in the unperfused capillary bed, which is caused by the greater perfusion distances and the lower pulmonary capillary blood volume in the acromegalic lung.

In conclusion, the current findings confirm and extend previous observations in acromegaly, suggesting that the lung is largely, and perhaps invariably, involved in this disease. The lack of a comprehensive histologic evaluation of the lung from acromegalic patients does not allow to draw definite conclusions on the amount and quality of pulmonary involvement in this disease. This approach could lead to the identification of an alveolar membrane or microvascular damage, at the level of which the primary cause of the functional alterations lies. Following this primary step, the role of smoke or other lung diseases should be investigated in this population, to estimate to what extent the natural course of the disease can be affected. On this basis, we propose to routinely incorporate the carbon monoxide diffusing capacity in the lung function assessment for a proper management of the disease.

Conflict of interest None.

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