Turk J Endocrinol Metab. 2021;25:151-157

# Pulmonary Function and Serum Carboxymethyl-Lysine Level Evaluation in Acromegaly Patients

## Akromegali Hastalarında Solunum Fonksiyonu ve Serum Karboksimetil-Lizin Seviyesinin Değerlendirilmesi

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## Abstract

**Objective:** We aimed to evaluate the pulmonary function tests (PFTs) and serum carboxymethyl-lysine (CML) level and their association with the disease activity in patients with acromegaly. **Material and Methods:** This cross-sectional study included 65 acromegalic patients (F/M:28/37) and 52 controls ( F/M:23/29). PFTs such as spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO) were performed to determine the lungs' ability to exchange gases. Serum CML levels were measured with the enzyme-linked immunosorbent assay. Basal and nadir growth hormone (GH), hemoglobin A1c (HbA1c), and insulin-like growth factor-1 (IGF-1) were also assessed. **Results:** Serum CML levels were significantly higher in acromegalic patients (208.1±80 ng/mL) than in controls (174.2±11 ng/mL), (p=0.02). The evaluated PFTs were expressed as predicted values [forced expiratory volume in the 1st second % (p=0.01), forced vital capacity % (p=0.007), functional residual capacity % (p=0.03), residual volume % (p=0.03), vital capacity % (p=0.007), total lung capacity % (p=0.01), and DLCO% (p=0.02)] that were found to be elevated in acromegalic patients than in controls. CML levels positively correlated with HbA1c (r=0.53, p=0.02) but did not correlate with basal GH levels (r=0.35, p=0.06). GH and IGF-1 levels positively correlated with lung volume in acromegalic patients. **Conclusion:** Serum CML levels increased in acromegaly patients but had no association with the PFTs results. Increased lung volume was the most prominent lung function alteration in acromegalic patients; relevantly, we found elevated GH and IGF-1 levels to be associated with the increased lung volumes. Future studies need to evaluate the association between the advanced glycation end-products and complications of acromegaly.

**Keywords:** Acromegaly; pulmonary function tests; growth hormone; insulin-like growth factor-1; carboxymethyl-lysine

## Özet

**Amaç:** Bu çalışmada akromegali hastalarında solunum fonksiyonları, serum karboksimetil-lizin [carboxymethyl-lysine (CML)] seviyeleri ve hastalık aktiviyeleriyle ilişkilerini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Bu kesitsel çalışmaya 65 akromegali hastası (K/E: 28/37) ve 52 kontrol (K/E: 23/29) olgusu dâhil edilmistir. Solunum fonksiyon testleri (SFT) spirometri ile gaz değişimi ise karbon monoksit difüzyon kapasitesi [diffusing capacity of the lungs for carbon monoxide (DLCO)] ile değerlendirilmiştir. Serum CML düzeyi enzim bağımlı immünosorbent ölçüm metoduyla ölçülmüştür. Hemoglobin A1c (HbA1c), insülin benzeri büyüme faktörü-1 [insulin-like growth factor-1 (IGF-1)], bazal ve nadir büyüme hormonu (BH) düzeyleri ölçülmüştür. **Bulgular:** Serum CML seviyeleri akromegali hastalarında (208,1±80 ng/mL), kontrol hastalarına göre (174,2±11 ng/mL) belirgin olarak daha yüksekti (p=0,02). SFT ve DLCO; akromegali hastalarında kontrol grubuna göre anlamlı olarak daha yüksek saptandı [% birinci saniyedeki zorlu ekspiratuar volüm (p=0,01), % zorlu vital kapasite (p=0,007), % fonksiyonel rezidüel kapasite (p=0,03), % kalıntı hacim (p=0,03), % vital kapasite (p=0,007), % total akciğer kapasitesi (p=0,01) ve %DLCO (p=0,02)]. CML düzeyi; HbA1c ile pozitif korelasyon gösterirken, (r=0.53, p=0.02), bazal BH ile korelasyon mevcut değildi (r=0.35, p=0.06). Akromegali hastalarında BH ve IGF-1 düzeyleriyle akciğer kapasitesi arasında pozitif korelasyon mevcuttu. **Sonuç:** Serum CML düzeyleri akromegali hastalarında yükselmiştir, ancak SFT ile arasında bir ilişki gösterilememiştir. Artmış akciğer kapasitesi akromegali hastalarında en sık görülen solunum fonksiyon değişikliğidir ve artmış BH ve IGF-1 düzeyleriyle arasında bir ilişki mevcuttu. İleri glikasyon son ürünleri ve akromegali komplikasyonları arasındaki ilişkinin gösterilebilmesi için daha fazla çalışmaya ihtiyaç vardır.

**Anahtar kelimeler:** Akromegali; solunum fonksiyon testi; büyüme hormonu; insülin benzeri büyüme faktörü-1; karboksimetil-lizin

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Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

**Received:** 02 Dec 2020 **Received in revised form:** 03 May 2021 **Accepted:** 25 May 2021 **Available online:** 08 Jun 2021



DOI: 10.25179/tjem.2020-80353

## Introduction

Long-term access of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) to tissues is responsible for the cardiovascular and respiratory changes in patients with acromegaly (1).

Mortality associated with respiratory disease is observed to be approximately threefold higher in patients with acromegaly than in healthy subjects. Respiratory disorders in acromegalic patients are the second leading reason for their mortality, responsible for 12-25% of deaths (1, 2). Previous studies have reported that acromegaly patients develop anatomical alterations; these alterations affect craniofacial bones, soft tissues, respiratory mucosa/cartilages, respiratory muscle activity, lung volumes, or rib cage geometry, which can change the respiratory functions of the patients. These abnormalities cause two considerable respiratory dysfunctions: Sleep apnea and impaired respiratory function (3).

Generally, respiratory changes are considered a part of systemic organomegaly. However, the pathophysiology of respiratory dysfunction is still unclear. Combining oxidative stress with the diminished antioxidant capacity is one of the underlying mechanisms of tissue damage in acromegaly (4). Also reported, an increase in advanced glycation end-products (AGEs) is due to increased oxidative stress in diseases, such as diabetes, rheumatoid arthritis, and chronic kidney failure (5). Recent studies state that AGEs may have a role in potentiating acromegaly pathophysiology (6). In vitro studies have shown that AGEs can stimulate human monocytes to secrete IGF-1 (7).

Studies yet do not have any clinical data considering the relation between serum AGEs and tissue function in acromegalic patients. Therefore, we assume that the respiratory functional alterations in the acromegalic lungs could be associated with elevated serum GH and AGEs. This study aimed at two objectives: 1) Evaluate respiratory functions and serum carboxymethyl lysine (CML) levels in acromegalic patients; and 2) Evaluate the respiratory functions' and serum CML level's association with the disease activity in acromegalic patients.

## Subjects and Methods

**Study Population:** In this cross-sectional study, we recruited 65 patients with acromegaly and 52 subjects without any lung disease. In addition, the study protocol was approved by the local ethics committee (2012.0150) of Marmara University School of Medicine. The subjects participating in this study had signed an informed consent form.

To proceed further in our study, we obtained anamnesis and performed a medical examination of each included subject. The term body mass index (BMI) in this study is calculated as the weight (kg) divided by height ($m^2$). We further categorized the subjects as smokers (at least one cigarette/day) and non-smokers. Each patient's biochemical tests, treatment (surgery, radiosurgery, and medical therapy), and hormone replacement data were acquired from their medical records. Fifty-two control subjects without any lung disease were recruited in this cross-sectional study.

**Pulmonary Function Tests:** Respiratory functions were evaluated using spirometry. The same technician performed all measurements according to the recent guidelines via the Sensor Medics Vmax229 (Sensormedics Corps., Yorba Linda, CA, USA) spirometry and gas dilution system.

The spirometer measured the forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV1), FEV1/FVC ratio, and forced mid-expiratory flow rate (FEF) (FEF 25-75%) parameters. Further, vital capacity (VC), expiratory reserve volume, residual volume (RV), and functional residual capacity (FRC) were measured by the nitrogen washout technique. Parameters such as total lung capacity (TLC), the ratio RV/TLC, and inspiratory capacity evaluated lung volumes. FVC >80% was considered normal. We found increased FVC in the first phase of interstitial pulmonary disease. However, the pathological values of increased FVC had no threshold values mentioned. We used the FEV1/FVC ratio to determine obstructive pulmonary disease. The study had no cut-off values for the pathological threshold of FEV1/FVC ratio, while the values above 70% were considered normal.

Next, we used diffusing capacity of the lungs for carbon monoxide (DLCO) to determine

gas exchange measurements. The values of 80-140% were considered normal, while DLCO >140% was associated with asthma, polycythemia, alveolar hemorrhage, and congestive heart failure.

We calculated alveolar volume (VA) and the corrected value of DLCO (DLCO/VA) by utilizing VA and diffusing capacity (DL) adjusted for lung volumes (DL/VA). The FEV1, FEV1/FVC ratio, FEF 25-75%, RV, and RV/TLC were utilized for obstructive pathology, whereas VC and TLC were used to determine the restrictive disorder. Using equations, we calculated the predicted values from a reference population of nonsmokers with age and height (8). The predicted value percentage was calculated by dividing the obtained predicted value by the raw value. Pulmonary function tests (PFTs) were evaluated by a single pulmonary disease specialist blinded to the patient's characteristics (Sait Karakurt).

**Biochemical Evaluation:** Basal GH (in the morning), nadir GH (the lowest GH achieved during the 2-h oral glucose tolerance test), and IGF-1 levels were measured. In acromegaly patients, we considered the disease controlled when nadir GH levels were below 1 ng/dL (1 µg/L), and the age-related IGF-1 was at a normal level; whereas, we considered the disease uncontrolled when nadir GH level was equal to or above 1 ng/dL (1 µg/L), and the elevated serum IGF-1 level was above the normal.

We studied GH and IGF-I levels in the patients by a chemiluminescent immunometric assay (IMMULITE2000, Siemens, USA). The calculated intra-assay and inter-assay variation coefficients were 3.5-4.2% and 6.5-6.6%, respectively.

Serum CML levels were evaluated with the enzyme-linked immunosorbent assay method. The CML kit had a value range of 20-3,000 ng/mL, while its sensitivity was 10.03 ng/mL. The intra-study and inter-study variability coefficients for the sensitivity concentration were 8% and 10%, respectively (Bioassay Technology Laboratory, E1413Hu, Shanghai, China).

We used high-performance liquid chromatography to evaluate serum hemoglobin A1c (HbA1c) levels. Also, the serum glucose levels were measured by the hexokinase method (Cobas 8000 Modular Analytics, Roche Diagnostics, Germany).

### Statistical Analysis

We used the SPSS (version 22.0, Chicago, IL) statistical package for Windows. According to the data distribution for the numerical variables' comparison between two groups, we chose the Student's t-test and Mann-Whitney U for statistical analysis. Either the Pearson's or Spearman's test was used for correlation analysis. In addition, the chi-square test was used for determining associations between the categorical variables. p values lower than 0.05 are statistically significant.

## Results

Demographic characteristics and biochemical test results of the subjects are listed in Table 1. The two groups had similar age, BMI, smoking status, and sex of the subjects. Mean values for basal GH (p=<0.01), nadir GH (p=<0.01), IGF-1 (p=<0.01), glucose (p=0.04), and HbA1c (p=0.02) were higher in acromegaly group than in control group. Serum CML levels were higher in the acromegaly group (208.1±80 ng/mL) than in the control group (174.2±11 ng/mL) (p=0.02). Table 2 illustrates the comparison of PFTs between the acromegalic patients and controls. The obstructive parameters; predicted % of FEV1 (p=0.01), FRC (p=0.007), RV (p=0.037), and restrictive parameters; and predicted % of FVC (p=0.007) and TLC (p=0.01) were significantly higher in acromegalic patients than in controls. Although acromegalic patients had lower diffusion parameters, DLCO was significantly higher in acromegalic patients than in controls (p=0.02).

Although a positive correlation existed either in serum CML levels or HbA1c levels (r=0.53, p=0.02), there was no significant correlation with basal GH level (r=0.35 p=0.06). In the study, serum CML levels were not associated with fasting plasma glucose, nadir GH, IGF-1, BMI, or any PFTs. Moreover, IGF-1, nadir GH, and basal GH levels showed positive correlations with obstructive and restrictive parameters of the PFTs (Table 3).

Table 1. Clinical and laboratory characteristics of acromegalic patients and controls.

| | Acromegalic patients (n=65) | Control group (n=52) | p value |
|---|---|---|---|
| Age (year) | 44.75±10.81 | 46.46±10.32 | NS |
| Female/male (%) | 28/37 (43.1/56.9) | 23/29 (44.2/55.7) | NS |
| Smoker/nonsmoker (%) | 13/49 (21/79) | 10/25 (28.6/71.4) | NS |
| BMI (kg/m2) | 29.77±4.2 | 28.95±4.51 | NS |
| SBP* (mmHg) | 127.05±19.92 | 126.41±17.63 | NS |
| DBP** (mmHg) | 79.76±12.29 | 79.30±13.78 | NS |
| Type 2 diabetes (%) | 18 (27.7) | 13 (25) | 0.03 |
| Hypertension (%) | 28 (43.1) | 0 (0) | 0.03 |
| Somatostatin analogue treatment (%) | 41 (63.1) | - | |
| Disease duration (month) | 66.23±65.96 | - | |
| Basal GH (ng/dL) | 8.6±10 | 0.2±0.1 | <0.01 |
| Nadir GH (ng/dL) | 5.97±15.31 | 0.10±0.11 | <0.01 |
| IGF-1 (ng/dL) | 394.26±253.27 | 122.25±44.91 | <0.01 |
| Fasting glucose (mg/dL) | 91.03±13.15 | 84.26±11.65 | 0.04 |
| HbA1c (%) | 5.56±0.82 | 5.22±0.67 | 0.02 |
| CML (ng/mL) | 208.1±80 | 174.2±11 | 0.02 |

NS: Not significant; BMI: Body mass index; *SBP: Systolic blood pressure; **DBP: Diastolic blood pressure; GH: Growth hormone; IGF-1: Insulin-like growth factor-1; HbA1c: Hemoglobin A1c; CML: Serum carboxymethyl-lysine.

Table 2. Obstruction, restriction, and gas exchange parameters of acromegalic patients and healthy controls.

| | Acromegalic patients (n=61) | Healthy controls (n=37) | p value |
|---|---|---|---|
| **Obstruction parameters** | | | |
| FEV1/FVC (%) | 79.77±6.12 | 79.40±6.71 | NS |
| FEV1 predicted % | 115.36±1.47 | 106.02±15.59 | 0.01 |
| FEF 25-75 (L/min) | 3.42±1.55 | 3.92±1.55 | NS |
| FEF 25-75 predicted % | 101.47±35.62 | 90.97±29.15 | NS |
| FRC predicted % | 160.67±66.46 | 136.71±36.23 | 0.03 |
| RV predicted % | 180.84±87.92 | 151.40±42.58 | 0.037 |
| Restriction parameters | | | |
| FVC predicted % | 120.72±18.04 | 110.94±15.58 | 0.007 |
| TLC predicted % | 137.89±31.62 | 122.40±19.98 | 0.01 |
| **Gas exchange (diffusion) parameters** | | | |
| RV/TLC | 40.27±11.75 | 39±7.34 | NS |
| DLCO | 144.50±31.90 | 133.40±43.00 | 0.02 |
| DLCO/VA predicted % | 115.56±21.89 | 121.64±28.74 | NS |
| VA predicted % | 123.98±30.55 | 109.78±19.81 | 0.007 |

NS: Not significant; FEV1: Forced expiratory volume in the 1st second; FVC: Forced vital capacity; FEF: Forced mid-expiratory flow rate; FRC: Functional residual capacity; RV: Residual volume; TLC: Total lung capacity; DLCO: Diffusing capacity of the lungs for carbon monoxide; VA: Alveolar volume.

## Discussion

This study shows the serum CML levels to be higher in acromegaly patients than in controls and not associated with the patients' lung volumes. Increased lung volumes have been the most prominent lung function alteration in acromegalic patients. Moreover, nadir GH, basal GH, and IGF-1 levels have shown positive correlations with the lung volume parameters and DLCO of acromegalic patients.

Table 3. Correlation coefficients of PFTs parameters and serum CML level with nadir growth hormone and insulin-like growth factor-1 levels.

| PFT parameters | Nadir GH | IGF-1 |
|---|---|---|
| FVC | | r=0.280 p<0.05 |
| FVC predicted % | r=0.293 p<0.005 | r=0.303 p<0.05 |
| FEV1 | | r=0.244 p<0.05 |
| FEV1 predicted % | r=0.245 p<0.05 | |
| VC | | r=0.238 p<0.05 |
| VC predicted % | r=0.344 p<0.005 | r=0.312 p<0.005 |
| RV predicted % | r=0.323 p<0.05 | r=0.327 p<0.005 |
| FRC | | r=0.252 p<0.05 |
| TLC | | r=0.234 p<0.05 |
| TLC predicted % | r=0.302 p<0.005 | r=0.344 p<0.005 |
| DLCO | | r=0.250 p<0.05 |
| DLCO predicted % | r=0.208 p<0.05 | r=0.297 p<0.005 |
| Serum CML (ng/mL) | r=0.35 p=0.06 | |

NS: Not significant; FEV1: Forced expiratory volume in the 1st second; FVC: Forced vital capacity; FEF: Forced mid-expiratory flow rate; FRC: Functional residual capacity; RV: Residual volume; TLC: Total lung capacity; DLCO: Diffusing capacity of the lungs for carbon monoxide; VA: Alveolar volume.

Large lung volumes in acromegalic patients were first reported by Cushing in 1927, in an autopsy series of four patients (9). Previous studies have shown increased lung volumes in acromegalic patients. However, their results cannot be considered definite due to the limited number of patients and lack of control groups. Therefore, such previous studies related to the lung function of acromegalic patients, with a small number of patients and the absence of a matched control groups, are of less significance.

Two previous studies with a small number of patients and without control groups demonstrated an increased lung volume in acromegalic male patients (10,11). Three other small studies without control groups have demonstrated an increased lung volume in gender-independent acromegalic patients (12,13,14). A small controlled study showed higher VC% and TLC% in acromegalic males than healthy subjects (15). However, these studies suggest that the increased lung volumes of acromegaly patients are associated with increased alveolar size rather than the alveolar number (15). In contrast, two small studies had demonstrated no increase in lung volumes (16,17). Nonetheless, a prospective study shows that increased lung volumes in acromegalic patients with active disease decreased after six months of therapy (18).

We lack adequate data to reveal the causes of increased lung volumes in acromegalic patients. The parameters such as lung compliance, transpulmonary pressure, and pulmonary muscle strength compliance were evaluated in some previous studies; however, we have not evaluated these parameters in our study. DLCO is a predictor of diffusion capacity and was elevated in the acromegaly group of this study. However, the lung volume adjusted diffusion parameter, i.e., DLCO/VA, was similar in both groups. Ventilation-perfusion match plays a more significant role in determining the DLCO than the diffusion itself; thus, the changes in alveolar volume affect DLCO. Moreover, increased volume reflecting high alveolar mass may increase the DLCO value that may be corrected with the Krogh constant (DLCO/VA). In this study, the similar Krogh constant in both groups suggests that an increased DLCO increased the lung volume rather than increasing the actual DLCO. This suggestion is further supported by the increased VA in acromegalic patients. Since CO used in measuring diffusion capacity has a very high affinity for hemoglobin (Hb), the diffusion capacity is affected by Hb value. Thus, we have adjusted the diffusion parameters for Hb values. Only a few studies have evaluated the DLCO, while it was expected in a majority of them. A single study

has reported decreased Krogh constant, while all other studies have reported the usual Krogh constant (11,12,15,18). Another study demonstrates that despite increased lung volumes, the DLCO and DLCO/VA were normal, and lung volumes decreased after therapy. At the same time, unchanged diffusion capacity suggests the reversibility of lung volumes.

Authors of previous studies have hypothesized that an increased alveolar size instead of an increased alveolar number was the primary cause of the enlarged lung volume in acromegaly patients (18). This study showed a positive correlation of GH and IGF-1 levels with some of the lung volume parameters. Moreover, the levels of DLCO and VA had increased more in acromegaly patients than in controls, but the two groups had no difference between their DLCO/VA values. These similar DLCO values corrected to VA proved that an increase in diffusion area results in high DLCO. Increased lung volumes were the most prominent lung function alteration in acromegalic patients of this study. Subsequently, a positive correlation of IGF-1, nadir GH, and basal GH levels with the lung volume parameters and DLCO in this study suggests that the elevated IGF-1 and GH levels are responsible for the increased lung volumes of the patients. Although increased lung volumes might have resulted from general organomegaly due to the increased GH and IGF-1 levels, this relationship has not yet been shown in our study. Only two studies investigated this association, but both failed to demonstrate the relationship (11,18). Our cross-sectional study is superior in terms of the number of patients. Studies have shown decreased lung volumes in GH deficient patients (19,20) and improved lung volumes after 12 months of GH therapy (19). Correlation analysis in this study suggests the role of elevated GH and IGF-1 levels in the pathogenesis of increased lung volumes. Nevertheless, more prospective follow-up studies after specific treatments are needed to confirm the issues suggested for the pathogenesis of increased lung volumes.

We have found that diffusion capacity increased in acromegalic patients, while it was similar between the two groups after adjusted for increased lung volumes. Moreover, this study has shown that the serum CML level was higher in acromegaly patients than in controls. The elevated levels of CML could be attributed to the high levels of HbA1c in acromegalic patients of the study; however, more extensive and detailed studies are needed to confirm the positive correlation between the serum CML and basal GH levels. In acromegaly patients, AGEs increased without an association with PFTs. Since this is a cross-sectional study, we cannot reach a cause-and-effect relation. In the study, the majority of the patients under somatostatin analog treatment might have affected these results.

## Conclusion

In acromegaly patients, the increased serum CML levels did not correlate with the PFTs results. Increased lung volume was the most prominent lung function alteration in acromegalic patients and was associated with elevated GH and IGF-1 levels. Further studies are required to evaluate the association between the AGEs and acromegaly complications.

## Source of Finance

This work has been supported by Marmara University Scientific Research Projects Coordination Unit under grant number SAG-C-TUP-010710-0212”

## Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

## Authorship Contributions

Idea/Concept: Dilek Gogas Yavuz, A. Serap Yalın; Design: Dilek Gogas Yavuz, A. Serap Yalın; Control/Supervision: Dilek Gogas Yavuz, A. Serap Yalın; Data Collection and/or Processing: A. Serap Yalın, Mehmet Yaşar, Sait Karakurt; Analysis and/or Interpretation: Melin Uygur, Dilek Gogas Yavuz; Literature Review: A. Serap Yalın, Dilek Gogas Yavuz, Melin Uygur; Writing the Article: A. Serap Yalın, Melin Uygur, Dilek Gogas Yavuz; Critical Review: Dilek Gogas Yavuz, Melin Uygur.

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