SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2021; 38 (2); e2021020 DOI: 10.36141/svdld.v38i2.10623

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Abstract Aim: In this study, we aimed to investigate the possible role of endotrophin, a profibrotic byproduct of collagen VI, in the complex process of fibrosis development in the disease group with pulmonary fibrosis among interstitial lung diseases.
Material and Method: When the patients' participation in the study were completed, smoking or alcohol drinking conditions, and family history were recorded. Their weights and heights were recorded and body mass index (BMI) was calculated. In every patient, Spirometry with bronchodilator testing, determination of single-breath DLCO, and plethysmographic measurement of thoracic gas volume and airway resistance were performed. Blood samples were obtained for the inflammation markers such as sedimentation rate, C-reactive protein (CRP), complete blood count, liver and renal function tests, and lactate dehydrogenase levels. Serum endotrophin levels were measured in all patients. **Results:** Thirty-five patients with interstitial lung disease who were having pulmonary fibrosis, 35 patients with interstitial lung disease without pulmonary fibrosis, and 20 control patients without any signs or symptoms of interstitial lung disease were included in the study. Age distribution was similar between groups. The fibrotic ILD group was more commonly smoker or ex-smoker compared with the non-fibrotic ILD patients or control cases. Fibrotic ILD patients were leaner, having significantly decreased total lung capacity, diffusion capacity, and higher LDH levels. In the comparison of the 3 study groups regarding the endotrophin levels, there was a significant difference between groups. The fibrotic and non-fibrotic patient groups were compared for the Endotrophin levels and the difference was also significant. However, there was not any significant difference regarding the endotrophin levels between control cases and non-fibrotic ILD patients. Smoked cigarette pocket x year showed a significant positive correlation and DLCO % and KCO % showed a significant negative correlation with the endotrophin levels. **Conclusion:** Serum endotrophin levels significantly increase in fibrotic ILD patients compared with the non-fibrotic ILD patients and control cases. Endotrophin may be suggested as a diagnostic marker in fibrotic interstitial lung diseases.

Keywords: Endotrophin, interstitial lung disease, pulmonary fibrosis, plethysmography

Introduction

Pulmonary fibrosis (PF) is the end stage of a wide variety of heterogeneous interstitial lung diseases, characterized by the destruction of the pulmonary parenchyma, the accumulation of the extracellular matrix, and dramatic changes in the phenotype of both fibroblasts and alveolar epithelial cells. More than 200 causes of pulmonary fibrosis have been identified to date, including genetic disorders, autoimmune diseases, toxins, drugs, radiation,

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environmental and occupational exposures, but the most common form is idiopathic pulmonary fibrosis (IPF). Other common causes of progressive pulmonary fibrosis include connective tissue disease, chronic hypersensitivity pneumonia, asbestosis, and other pneumoconioses , sarcoidosis, and exposure to drugs such as bleomycin, amiodarone, or methotrexate. Although these conditions tend to have a more cautious disease course than IPF, they are associated with significant morbidity and a marked reduction in life expectancy (1). Current pathogenetic theories show that the fibrotic lung shares many common features with the aging lung, including genomic instability, telomere destruction, cellular aging, and mitochondrial dysfunction. Currently, there is a large body of evidence supporting the role of both natural and adaptive immunity in disease pathogenesis, both in the experimental models and in human lung fibrosis (2,3).

IPF predominantly takes place in middle-aged and older adults and accounts for 20 to 30% of interstitial lung diseases. It is usually progressive and can result in respiratory failure and death. In the pathogenesis of IPF, there are irregular fibroproliferative damage and repair in response to alveolar epithelial injury. Although the median survival for IPF is 3-5 years, each patient with IPF exhibits a different clinical course. New therapeutic agents have been developed that inhibit the progression of IPF containing Pirfenidone and Nintedanib (4,5). However, since the introduction of these drugs, the demand for useful biomarkers with potential for early diagnosis and the development of therapeutically effective and reliable agents has also increased. Although many exciting agents have been reported as biomarkers for IPF, IPF-specific biomarkers are still not in use in international clinical practice (6). Therefore, biomarkers are highly anticipated to diagnose IPF, monitor its progress, and predict its prognosis.Soon, biomarkers can potentially improve diagnostic accuracy and predictability of prognosis, thereby contributing to the identification of optimal treatment strategies and the evaluation of therapeutic effectiveness.

Col VI (collagen 6) is known to have essential roles in extracellular matrix remodeling. In the lung, Col VI is a component of the basement membrane and provides flexibility and mechanical support (7). A recent study has shown that the failure of Col VI secretion in mice was associated with a decrease in cell-extracellular matrix interactions in the lung, which affects modified basement membrane structure and lung elasticity (8). Endotrophin is a fragment of type VI collagen and it has been shown to modulate cell-cell interactions, stimulate proliferation of mesenchymal cells, and prevent cell apoptosis. Endotrophin stimulates the production of transforming growth factor-beta 1 (TGF-B1), adipose tissue fibrosis, and increases insulin resistance. Endotrophin performs several functions in many tissues (9).

In this study, we aimed to investigate the possible role of endotrophin, a profibrotic byproduct of collagen VI, in the complex process of fibrosis development in the disease group with pulmonary fibrosis among interstitial lung diseases.

Material and Methods

This prospective study was performed in Suat Seren Chest Disease and Thorax Surgery Research and Training Hospital, Esrefpasa Metropolitan Municipality Hospital, and Tire Public Hospital. Okmeydanı Research and Training Hospital Local ethics committee approved the study and informed consent was obtained from all of the participants. Inclusion criteria for the study were as follows: 1) Those newly diagnosed with pulmonary fibrosis (IPF or due to any other interstitial lung disease such as NSIP fibrosing type, RA, Progressive Systemic Sclerosis, Asbestosis, Chronic Hypersensitivity Pneumonia, Drug-induced fibrosis, Sarcoidosis, and etc.), 2) Newly diagnosed interstitial lung disease with no pulmonary fibrosis, 3) Patients giving consent, 4) Those between the ages of 25-90 years.

Exclusion criteria were as follows:1) Malignancy, 2) Those with an autoimmune disease, 3) Chronic kidney disease, 4) Chronic heart disease, 5) Liver cirrhosis, 6) Serious infections, 7) Glitazone use (lowering endotrophin level), 8) Pregnancy, 9) Patients who do not give consent

All participants were newly diagnosed patients. Serum endotrophin levels were measured in all patients. For the endotrophin molecule, the blood was taken to the yellow biochemistry tube, after the centrifugation process was done; the supernatant was taken to the Eppendorf tube and stored at -80 degrees.

Patients without any comorbidity who applied to the Pulmonology department outpatient clinic for

control were included as the control group. The control group had no occupational-environmental exposure or family history.

When the patient's participation in the study was completed, smoking or alcohol drinking condition, and family history were recorded. Their weights and heights were recorded and body mass index (BMI) was calculated with the formula BMI=weight/height^2.

In every patient, Spirometry with bronchodilator testing, determination of single-breath DLCO, and plethysmographic measurement of thoracic gas volume and airway resistance (Vmax 229 AutoBox; Sensormedics Inc., Yorba Linda, CA, USA) were performed following the criteria of European Respiratory Society (10). Blood samples were obtained for the inflammation markers such as sedimentation rate, C-reactive protein (CRP), complete blood count, liver and renal function tests, and lactate dehydrogenase levels.

The patients were diagnosed by evaluating the radiological findings, anamnesis, environmental exposure histories, bronchoalveolar lavage and laboratory data together. According to the presence of fibrosis in high resolution computerized tomography (HRCT), fibrotic and non-fibrotic ILD groups were determined. In HRCT, fibrosis was defined as bronchovascular distortion, traction bronchiectasis, reticular opacities, and volume loss in the lung and these patients were included in the fibrotic ILD group. The patients with basal ground glass opacity, mosaic attenuation or nodular lesions in the absence of fibrosis in HRCT were included in the non-fibrtic ILD group (10). Radiological patterns (fibrosis, ground glass opacity, mosaic attenuation, and etc.) were evaluated separately in both groups of patients. With the decision of the multidisciplinary council, lung biopsy was performed in patients who could not be diagnosed with these data.

High resolution computerized tomography (HıthachıWhole Body X-ray System, Hıthachı, Ltd. 2-16-1, Highashi-Ueno, Taito-ku, Tokyo, 110-0015, Japan) was performed in supine position, on full inspiration, with 16 detectors and 1.25 mm section thickness. Thorax HRCT of all patients were examined by two independent radiologists.

Serum endotrophin levels were measured in all patients. For the endotrophin molecule, the blood was taken to the yellow biochemistry tube, after the centrifugation process was done; the supernatant was taken to the Eppendorf tube and stored at -80 degrees. When all patients' participation was completed, all blood samples were evaluated for the endotrophin levels as per the manufacturer's guideline. Serum endotrophin levels were measured using an enzyme-linked immunosorbent assay (ELISA); human endotrophin ELISA kits (Sunred Biological Technology Catalogue No:201–12-9305) were used.

Statistical Analyses

SPSS version 21.0 (SPSS Inc, Chicago Illinois) statistical program was performed. The parametric variables were expressed with mean ± standard deviation, while categorical variables were expressed with percentage (%). In the comparison of parametric data between two independent groups, an independent sample t-test was performed. For non-normally distributed data, the analysis was performed with the Mann-Whitney U test. In more than two group comparisons; One-Way Anova and Bonferroni post-hoc analysis were used for parametric data, and Kruskal-Wallis and Dunnett-T3 post-hoc analysis method was used for nonparametric data. Spearman correlation analysis was performed to determine the association of serum endotrophin levels with age, BMI, smoking history, and spirometry findings in ILD patients with or without fibrosis. The significance level was set at $p<0.05$. ROC curve was created to evaluate the role of endotrophin level in fibrotic and nonfibrotic ILD patients.

Results

Thirty-five patients with interstitial lung disease who were having pulmonary fibrosis, 35 patients with interstitial lung disease without pulmonary fibrosis, and 20 control patients without any signs or symptoms of interstitial lung disease were included in the study.

The distribution of the interstitial lung diseases in patient groups was as follows;

In fibrotic group: 13 IPF, 11 chronic hypersensitivity pneumonia, 9 unclassified ILD, and 2 asbestosis

In non-fibrotic group: 15 chronic akut hypersensitivity pneumonia, 10 unclassified ILD, 1 asbestosis, 1 pulmonary involvement of connective tissue disease, 4 respiratory bronchiolitis associated pneumonia, 1 NSIP, 2 Langerhans cell histiocytosis, and 1 sarcoidosis

General characteristics of the study participants are summarized in Table 1. Age distribution was similar between groups. Family history was present in only the fibrotic ILD group. Alcohol consumption was more common in the fibrotic ILD group. The fibrotic ILD group was more commonly smoker or ex-smoker.

Body mass index, spirometry findings, and laboratory data of fibrotic and non-fibrotic ILD groups are compared in Table 2. Fibrotic ILD patients were leaner, having significantly decreased total lung capacity, diffusion capacity, and higher LDH levels.

Thorax CT findings in patients with ILD are summarized in Table 3. Thorax CT findings were diffuse/subpleural/central, in 21/3/11 patients in the non-fibrotic ILD group and 8/27/0 patients in the fibrotic ILD group, respectively. Hilar lymphadenopathy was present in 1 patient of the non-fibrotic ILD group and 3 patients of the fibrotic ILD group.

Bronchoalveolar lavage findings are summarized in Table 4. Mix alveolitis was significantly more common in fibrotic ILD patients compared with the non-fibrotic ones.

The distribution of Endotrophin was non-normal. For that reason, the comparisons were per-

Table 1. General characteristics of the study participants

	Control group (n:20)	Non-fibrotic ILD (n:35)	Fibrotic ILD (n:35)	p-value
Gender (Female/Male)	11/9	14/21	25/10	**0.012**
Age (years)	59.65 ±8.84	59.54 ±10.80	62.68±8.32	0.35
Family history (n)	0	0	2	**0.001**
Alcohol	0	1	4	**0.001**
Smoking history No/quit smoking/still smoker	10/7/3	14/7/14	9/19/7	**0.012**
Smoking (pocket x year)	20.60±19.07	17.29±15.87	30.93±22.44	**0.01**

Table 2. Comparison of fibrotic and non-fibrotic ILD groups for laboratory data

	Non-fibrotic ILD (n:35)	Fibrotic ILD (n:35)	p-value
BMI (Kg/ m^2)	30.35 ±5.73	26.40 ±4.44	**0.003**
FEV1 (%)	84.45 ±18.18	83.71±21.94	0.88
FVC (%)	82.38±18.71	77.68±18.82	0.32
FEV 1/FVC%	85.93±7.22	85.43±7.05	0.74
VC (%)	83.61±19.52	77.46±20.75	0.44
TLC (%)	85.80±17.71	74.25±17.90	**0.012**
DLCO (%)	69.74±21.91	49.31±16.53	**0.001**
KCO (%)	86.09±24.65	71.56±30.53	**0.001**
SPO2%	95.58 ±2.09	94.06 ±2.36	0.19
Sedimentation (mm/hour)	25.59 ±11.77	24.03 ±10.30	0.71
CRP (mg/L)	1.01±0.95	0.63±0.57	0.32
WBC (10^3/μL)	7781.61±1874.10	8368.42±1708.58	0.21
NLR	2.35 ± 0.94	2.11 ± 0.85	0.11
Eosinophilia (10^3/μL)	258.57± 130.23	293.75 ± 129.50	0.28
Creatinine (mg/dL)	0.76± 0.27	0.92 ±0.24	0.21
AST (U/L)	21.20±14.70	27.11±36.59	0.48
LDH (U/L)	197.17±39.05	224.11±36.50	**0.004**

BMI: Body mass index, VC: Vital capacity, TLC: Total lung capacity, DLCO: Single-breath carbon monoxide diffusing capacity, KCO: The rate constant for carbon monoxide uptake from alveolar gas, CRP: C-reactive protein, WBC: White blood cell count, NLR: Neutrophil-lymphocyte ratio, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase

Table 3. Thorax CT findings of patients with ILD

	Non-Fibrotic ILD (N:35)	Fibrotic ILD (N:35)	p-value
Ground Glass Appearance	31	15	**0.001**
Fibrosis	-	25	
Mosaic Perfusion	17	6	
Honeycomb Appearance	-	14	
Centrilobular Nodule	19	2	
Traction Bronchiectasis	-	17	
Cysts / Cavity	7	11	

Table 4. Bronchoalveolar lavage findings

	Non-Fibrotic ILD (N:35)	Fibrotic ILD (N:35)	p-value
Normal	16	20	**0.001**
Neutrophilic alveolitis	4	3	
Lymphocytic alveolitis	4	4	
Mix alveolitis	1	4	
BAL was not performed/non-diagnostic	8	3	
Contaminated	2	0	

formed with the non-parametric tests. In the comparison of the 3 study groups (Kruskal-Wallis test), there was a significant difference between groups (p: 0.034). The fibrotic and non-fibrotic patient groups were compared for the Endotrophin levels (Mann-Whitney U test) and the difference was also significant (p: 0.023). However, there was not any significant difference regarding the endotrophin levels between control cases and non-fibrotic ILD patients (p: 0.69) (Figure 1).

Association of serum endotrophin levels with age, BMI, smoking history, and spirometry findings in ILD patients with or without fibrosis was determined with the Spearman's correlation analysis (Table 5). Smoked cigarette pocket x year showed a significant positive correlation and DLCO % and KCO % showed a significant negative correlation with the endotrophin levels.

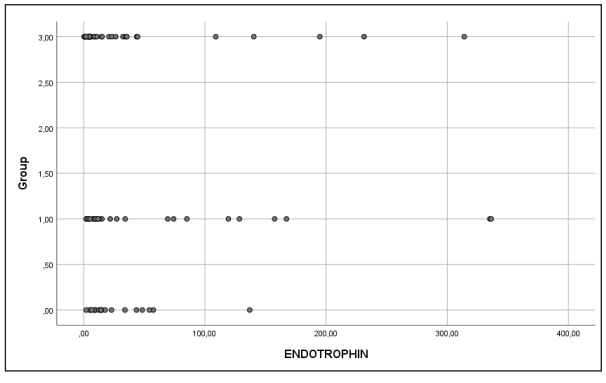

Figure 1. Dot plot showing the distribution of serum Endotrophin levels between groups

When the correlation between serum endotrophin and DLCO and KCO levels in fibrotic ILD patients was analyzed; There was negative correlation

Table 5. Association of serum endotrophin levels with the clinical findings

	Serum endotrophin levels	
	r	p
Age (Years)	-0.101	0.365
BMI (Kg/ m²)	-0.200	0.116
Smoking history	0.159	0.151
Pocket x year	**0.253**	**0.021**
FEV1 (%)	0.058	0.65
FVC (%)	0.081	0.526
FEV 1/FVC%	0.049	0.702
VC (%)	0.037	0.77
TLC (%)	-0.039	0.76
DLCO (%)	-0.297	**0.018**
KCO (%)	-0.329	**0.009**
SPO2%	0.121	0.343

BMI: Body mass index, VC: Vital capacity, TLC: Total lung capacity, DLCO: Single-breath carbon monoxide diffusing capacity, KCO: The rate constant for carbon monoxide uptake from alveolar gas.

with DLCO (p: 0.031), no correlation with KCO (p: 0.079).

Receiver operating characteristic (ROC) curve was drawn for serum endotrophin levels in fibrotic and nonfibrotic ILD differentiation (Figure 2). The area under the curve for serum endotrophin level was 0.728. Its endotrophin level was 22.725, its sensitivity was 0.493 and its specificity was 0.821.

Discussion

In this study, we analyzed the role of endotrophin levels as a biomarker for interstitial lung diseases and the presence of fibrosis in ILD and we determined that, in fibrotic ILD patients, endotrophin levels were significantly higher than that of the non-fibrotic ILD patients or control cases. Moreover, there was a significant negative correlation between the endotrophin levels and DLCO and KCO values. To the best of our knowledge, this is the first study in the literature reporting the elevated endotrophin levels in fibrotic ILD patients.

Collagen VI is primarily associated with the extracellular matrix of skeletal muscle and mainly stabilizes the cell membrane in muscle tissue. It is present in numerous cell types and has many different roles in different tissues. It also inhibits oxidative damage and apoptosis and regulates cell differentiation (12,13). The main pathogenetic mechanism in pulmonary fibrosis is the fibroblast activation and proliferation causing disturbances of extracellular matrix protein deposition. Previously, Specks et al (14) reported that Collagen VI expression was increased in lung fibrosis. Recently, in an experimental study Ucero et al reported that Type VI collagen produced by macrophages was up-regulated in fibrotic lungs and the Collagen VI mRNA positively correlated with fibrosis in IPF patients (15). In another experimental study, Okawa et al reported that type VI collagen was extremely up-regulated during sepsis in the rat lung within the first 24 h of lipopolysaccharide administration and they suggested that activation of Col VI might be involved in sepsis-mediated lung fibrosis (16). In the light of all these data, we can suggest that Collagen VI exerts a highly important role in pulmonary fibrosis that takes place due to some different reasons.

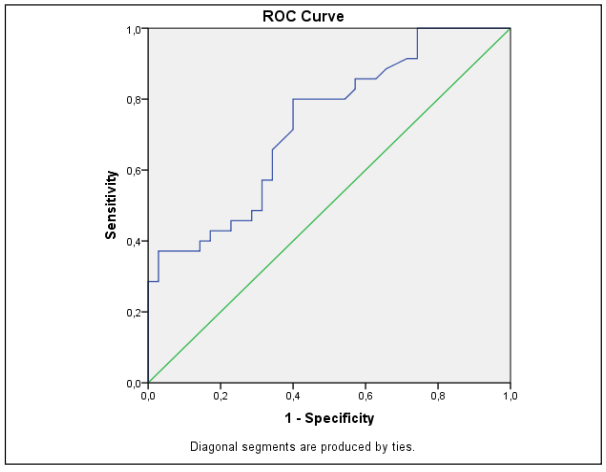

Figure 2: ROC curve for serum endotrophin level in fibrotic and non-fibrotic ILD differentiation

Endotrophin is a cleavage product of collagen VI. Endotrophin is an adipokine and exerts a major influence on adipose tissue, resulting in systemic elevation of pro-inflammatory cytokines (17). Recently, Ronnow et al (18) reported that increased endotrophin levels were associated with mortality in COPD which may be an indicator of an over-active repair process and fibrosis (18). We also determined significantly higher endotrophin levels in fibrotic ILD patients compared with the non-fibrotic ILD patients or control cases. The role of this pro-fibrotic cytokine in the pathogenesis of ILD should be evaluated in further studies.

Fibrotic ILD patients were leaner, having significantly decreased total lung capacity, and diffusion capacity. Moreover, their smoking history was more prominent and there was a significant positive correlation between smoked cigarettes pocket x year and serum endotrophin levels. Smoking-related interstitial fibrosis is known for years (19, 20). In that aspect, this positive correlation is important in defining the pathophysiological mechanisms of smoking-related interstitial fibrosis. On the other hand, we determined a significant negative correlation between the endotrophin levels and DLCO % and KCO %. The single-breath carbon monoxide diffusing capacity (DL_{CO}) is the product of two measurements during breath holding at full inflation: the rate constant for carbon monoxide uptake from alveolar gas (K_{CO} [$minute^{-1}$]) and the alveolar volume (V_A) (20). The prognostic significance of DL_{CO} and KCO has been mentioned in diffuse parenchymal lung diseases (22,23). The negative correlation determined between the endotrophin levels and DLCO % and KCO % may be showing the prognostic role of endotrophin in fibrotic interstitial lung diseases.

There are some limitations of this study. First is the low number of patients in study groups. Since the number of patients was low, the patients in different disease sub-groups were also low and we could not compare them. Secondly, we did not know the disease stages and for that reason, we could not comment on the role of endotrophin in lung fibrosis at early or late phases.

In conclusion, serum endotrophin levels significantly increase in fibrotic ILD patients compared with the non-fibrotic ILD patients and control cases. Endotrophin may be suggested as a diagnostic marker in fibrotic interstitial lung diseases. Various studies have shown the value of biomarkers in diagnosing, monitoring, and predicting the prognosis of patients with pulmonary fibrosis. Biomarkers such as endotrophin can potentially increase early diagnosis, diagnostic accuracy, and predictability of prognosis, thereby contributing to the identification of optimal treatment strategies and the evaluation of therapeutic efficacy. Further, larger prospective studies with longer follow-up periods and experimental studies are warranted to determine the role of endotrophin in lung fibrosis, especially in pathogenesis.

Competing interests: All the authors declare that there are no financial or non-financial competing interests.

Author Contributions: All of the authors provided critical review, relevant edits, and feedback to direct content during multiple rounds of review. In addition, all authors have read and approved the final version of this manuscript.

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