

Serum endocan levels in patients with stable COPD

Aylin Pihitili¹
Zuleyha Bingol²
Esen Kiyan²

¹Department of Pulmonary Medicine, Bezmialem Vakif University, Faculty of Medicine, Istanbul, Turkey;

²Department of Pulmonary Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Background: Endothelial cell specific molecule-1, also called as endocan, is a dermatan sulfate proteoglycan, which is expressed by endothelial cells in alveolar walls of the lung and kidney. High endocan levels are found associated with endothelial dysfunction and inflammation. We hypothesize that endocan level is also high in COPD due to systemic inflammation and endothelial dysfunction. We aimed to investigate the expression of endocan in patients with stable COPD.

Material and methods: The study included patients with COPD and control subjects. COPD patients were classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 criteria. Demographics, body mass index, smoking history, and comorbidities were recorded. Endocan levels of COPD patients and controls were compared.

Results: Totally, 88 subjects (47 stable COPD patients, 41 controls) were evaluated. Endocan levels were significantly higher in COPD patients than control group (860.1 ± 259.8 vs 647.3 ± 316.9 pg/mL, $P=0.001$). There was no relationship between GOLD COPD categories and endocan levels. Also endocan levels were similar between COPD patients with or without hypoxemia.

Conclusion: Serum endocan level was significantly higher in patients with stable COPD. Further studies should be performed to better understand the relationship between endocan and COPD.

Keywords: chronic obstructive pulmonary disease, endothelial cell specific molecule-1, endothelial dysfunction, systemic inflammation

Introduction

COPD is a chronic inflammatory lung disease that affects small airways, lung parenchyma, and vascular endothelium.¹⁻⁴ COPD is not a disease that affects only the lungs; it is a systemic inflammatory and endothelial disease.^{1,5-8}

Endothelial cell specific molecule-1, also called as endocan, is a dermatan sulfate proteoglycan, which is expressed by endothelial cells in alveolar walls of the lung and kidney.^{9,10} Endocan plays an important role in many endothelial-dependent pathophysiological situations, such as inflammation, tumor progression, cell proliferation and adhesion, migration, and angiogenesis.¹¹⁻¹⁵ In certain studies, high endocan levels were associated with endothelial dysfunction and inflammation.¹⁶⁻³⁴ Therefore, endocan was considered as a potential marker for endothelial dysfunction.^{11,15} There are several studies showing increased endocan levels in lung diseases such as lung cancer, acute lung injury, acute respiratory distress syndrome, community-acquired pneumonia, pulmonary embolism, obstructive sleep apnea (OSA), sarcoidosis, and pleural effusion.²⁵⁻³⁴ In the literature, there is no study about endocan level in patients with COPD. We hypothesize that endocan level is high in COPD, which is associated with systemic inflammation and endothelial dysfunction.

Correspondence: Esen Kiyan
Department of Pulmonary Medicine,
Istanbul Medical Faculty, Istanbul
University, 34360 Capa, Istanbul, Turkey
Tel +90 212 414 2000
Fax +90 212 414 2271
Email kiyanesen@gmail.com

This study aimed to investigate the serum endocan levels in COPD. Secondary aim was to evaluate the relationship between endocan levels and severity of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD categories, and hypoxemia.

Materials and methods

This prospective study included stable COPD patients admitted to the outpatient clinic of Istanbul University Istanbul Medical Faculty from January 2017 to January 2018. Age- (40–80 years) and gender-matched subjects without COPD or uncontrolled chronic diseases were included as a control group. Control subjects were selected from the relatives of the subjects who were admitted to our outpatient clinic. All of the subjects voluntarily signed their informed consent. The study was carried out according to the principles of the Helsinki Declaration. It was approved by Istanbul University Istanbul Medical Faculty Institutional Board (Ethic no 2014/1715).

We included adult patients (>18 years) with COPD diagnosis for at least 1 year and stable disease for 3 months without any change in the medication. The exclusion criteria were restrictive pulmonary diseases, significant cardiac failure, acute coronary syndromes (unstable angina pectoris and myocardial infarction), valvular heart diseases, congenital heart disease, renal or hepatic dysfunction, active inflammatory diseases, acute infections, malignancies, and medication that can potentially interfere with level of endocan (lipid lowering therapy, vitamins, or antioxidants).

Demographics such as body mass index (BMI), smoking history, spirometric parameters, and comorbidities were recorded. COPD patients were classified according to the GOLD 2017 recommendations considering symptoms and exacerbation risk to grade disease severity into categories A–D.³⁵ Significant hypoxemia was considered when partial arterial oxygen pressure <60 mmHg.

Serum endocan measurements

Blood samples were collected using EDTA as anticoagulant in the morning between 7.00 and 9.00 am. Blood samples centrifuged within 30 minutes of sampling at 1,500 g for 15 minutes and stored at –80°C until testing. Serum endocan level was measured by enzyme-linked immunoassay (ELISA) using a commercially available kit (Elabscience Biotechnology Inc, Houston, TX, USA) according to the manufacturer's instructions. The results are presented in pg/mL.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 software (AIMS, Istanbul, Turkey). All continuous variables are presented as the mean \pm SD and categorical variables as frequency (percentage). The concordance of normal distribution of all variables was calculated with the Shapiro–Wilk test. If the data were not normally distributed, we used nonparametric tests for dependent variables. Comparisons between two groups were carried out with Mann–Whitney *U*-test or Student's *t*-test. Categorical variables were compared with the chi-squared test. Comparison between more than two groups was done with one-way analysis of variance test. The Spearman correlation coefficient was used to examine the relationship between endocan and age, BMI, spirometric measurements, and comorbidities. A *P*-value of <0.05 was considered statistically significant.

Results

Totally, 47 COPD patients and 41 controls were included in the study. According to GOLD COPD classification, 38.3% (n=18) of our patients were in category B, 31.9% (n=15) in category D, and 29.8% (n=14) in category C. Comparison of the demographics and endocan levels of COPD patients and controls are presented in Table 1.

The distribution of endocan levels for COPD patients and control subjects was given in Figure 1.

Serum endocan levels were significantly higher in COPD patients than controls (860.1 \pm 259.9 vs 647.3 \pm 316.9 pg/mL *P*=0.001). There were seven females (four COPD patients and three control subjects) in our study. When we excluded female patients and control subjects, endocan levels were still significantly different between patients with COPD

Table 1 Differences between COPD patients and controls

Characteristics	COPD patients (n=47)	Control subjects (n=41)	P-value
Age (years)	61.5 \pm 8.7 Range: 40–75	59.7 \pm 9.7 Range: 43–79	0.4
Gender (female/male)	4/43	3/38	0.9
BMI (kg/m ²)	25.0 \pm 2.9	26.0 \pm 1.9	0.06
Smoking history (pack years)	36.3 \pm 17.2	30.0 \pm 20.1	0.09
Comorbidities (%) (hypertension and/or diabetes)	25.5	19.5	0.6
Endocan level (pg/mL)	860.1 \pm 259.9	647.3 \pm 316.9	0.001

Abbreviations: BMI, body mass index; Endocan, endothelial cell specific molecule-1.

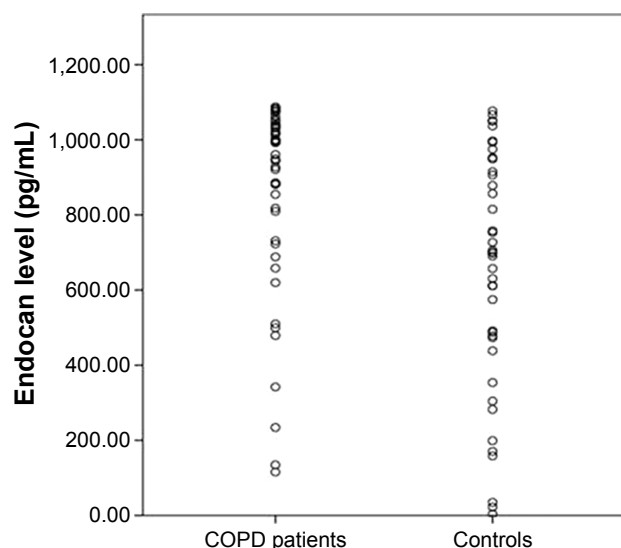


Figure 1 The distribution of endocan levels in COPD patients and control subjects.

and control subjects (847.1 ± 267.2 vs 654.2 ± 307.8 pg/mL, $P=0.002$). When COPD category progresses toward B to D, endocan levels tended to increase, but there was no statistically significant difference between COPD GOLD categories (group B: 820.9 ± 280.8 pg/mL, group C: 867.6 ± 236.8 pg/mL, group D: 900.3 ± 265.2 pg/mL). Comparison of COPD GOLD categories are presented in Table 2.

There were 17 patients with COPD who had significant hypoxemia. All of them were receiving long-term oxygen therapy (LTOT) and ten of them were also using noninvasive mechanical ventilation (NIMV) in addition to LTOT. There was no statistically significant difference between hypoxemic COPD patients and nonhypoxemic COPD patients in terms of endocan levels (921.2 ± 252 vs 825.5 ± 262.0 pg/mL, $P=0.2$). Comparisons of COPD patients with and without hypoxemia

are given in Table 3. Endocan levels were similar in patients who were receiving NIMV and the others who were not (863.6 ± 315.8 vs 859.2 ± 247.7 pg/mL, $P=0.9$).

There were 12 COPD patients with comorbidities (8 had hypertension, 2 had diabetes mellitus, 2 of them had both hypertension and diabetes). COPD patients with comorbidities had slightly higher but not significantly different endocan levels than those without comorbidities (910.8 ± 207.3 vs 842.8 ± 276.2 pg/mL, $P=0.4$). Comparisons of COPD patients with and without comorbidities are given in Table 4.

There was no correlation between endocan level and forced expiratory volume 1 second percent ($FEV_1\%$), forced vital capacity percent, age, BMI, comorbidities, LTOT, and NIMV.

Discussion

In this study, serum endocan level was found significantly higher in stable COPD patients than the control group. To our knowledge, this is the first study in the literature that investigates the endocan levels in stable COPD patients. COPD is associated with vascular endothelial dysfunction and systemic inflammation. For this reason, we wanted to investigate endocan levels in COPD and speculate that higher levels of endocan in COPD might be associated with inflammation and/or endothelial dysfunction.

It is known that endocan is expressed by pulmonary and renal endothelial cells. It is secreted by vascular endothelial cells, and also expression of endocan is regulated by a number of proangiogenic factors such as vascular endothelial growth factor as well as cytokines.^{9–11,36} Previous studies mentioned that endocan not only plays a role in the inflammatory process but also plays a role in the vascular damage and endothelium-dependent pathological disorders. Therefore, it

Table 2 Comparison of COPD GOLD categories

Characteristics	COPD group B (n=18)	COPD group C (n=14)	COPD group D (n=15)	P-value
Age (years)	60.5±9.1	63.4±9.1	60.9±9.8	0.6
Gender (female/male)	2/16	0/14	2/13	0.3
BMI (kg/m ²)	26.4±2.2	24.7±2.4	23.7±3.3	0.01
Smoking (pack years)	33.4±14.7	33.6±15.6	43.3±21.0	0.3
FEV ₁ (%)	62.0±6.0	36.1±11.7	29.7±11.5	<0.001
FVC (%)	74.4±8.2	52.9±12.3	44.9±16.9	<0.001
PaO ₂ (mmHg)	76.7±6.3	68.7±12.3	61.0±1.0	<0.001
PaCO ₂ (mmHg)	39.1±4.0	44.9±7.6	51.2±9.2	<0.001
Comorbidities (%)	22.2	42.9	13.3	0.2
Endocan level (pg/mL)	820.9±280.8	867.6±236.8	900.3±265.2	0.6

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PaCO₂, partial arterial carbon dioxide pressure; PaO₂, partial arterial oxygen pressure.

Table 3 Differences between COPD patients with and without significant hypoxemia

Characteristics	With hypoxemia (n=17)	Without hypoxemia (n=30)	P-value
Age (years)	61.8±10.0	61.3±8.2	0.9
Gender (female/male)	2/15	2/28	0.2
BMI (kg/m ²)	23.7±3.3	25.8±2.3	0.03
Smoking (pack/years)	37.1±18.2	35.9±17.0	0.2
FEV ₁ (%)	29.8±10.8	52.0±15.3	<0.001
FVC (%)	44.3±15.0	66.6±14.2	<0.001
PaO ₂ (mmHg)	59.1±9.8	75.0±7.6	<0.001
PaCO ₂ (mmHg)	52.7±8.3	40.1±4.2	<0.001
Comorbidities (%)	11.8	33.3	0.2
Endocan level (pg/mL)	921.2±252.0	825.5±262.0	0.2

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume 1 second; FVC, force vital capacity; PaCO₂, partial arterial carbon dioxide pressure; PaO₂, partial arterial oxygen pressure.

may represent a novel endothelial cell dysfunction marker.^{12–34} Since COPD is a systemic inflammatory disease that can affect vascular endothelium, increase of endocan it is expected. As expected, increased endocan level was shown in our study.

There are several studies in which endocan levels were investigated in lung diseases. Most of these previous studies were performed in patients with acute pulmonary diseases such as acute lung injury, acute respiratory distress syndrome, community-acquired pneumonia, pulmonary embolism, lung cancer, and pleural effusion.^{25–32} There are only two studies in

Table 4 Differences between COPD patients with and without comorbidities

Characteristics	With comorbidities (n=12)	Without comorbidities (n=35)	P-value
Age (years)	66.8±4.9	59.6±9.0	0.01
Gender (female/male)	1/11	3/32	0.9
BMI (kg/m ²)	25.9±2.5	24.7±2.9	0.2
Smoking (pack years)	37.0±16.5	36.1±17.6	0.8
FEV ₁ (%)	43.6±15.4	44.1±18.4	0.9
FVC (%)	58.7±16.6	58.5±18.7	0.9
PaO ₂ (mmHg)	72.8±11.1	67.1±12.6	0.7
PaCO ₂ (mmHg)	41.3±5.1	45.8±9.1	0.1
LTOT (%)	16.7	42.9	0.2
NIMV (%)	8.3	25.7	0.4
Endocan level (pg/mL)	910.8±207.3	842.8±276.2	0.4

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume 1 second; FVC, forced vital capacity; LTOT, long-term oxygen therapy; NIMV, noninvasive mechanical ventilation; PaCO₂, partial arterial carbon dioxide pressure; PaO₂, partial arterial oxygen pressure.

stable lung diseases, sarcoidosis and OSA.^{33,34} These studies reported higher endocan levels in sarcoidosis and OSA.^{33,34} Aciksari et al³⁴ reported that sarcoidosis is associated with high levels of endocan and lower flow-mediated dilation values, which may indicate endothelial dysfunction and an early stage of atherosclerosis. According to these results, they concluded that it may be a prognostic marker for both the inflammatory process and the endothelial function.³⁴ However, they could not show any difference for endocan levels between stages of sarcoidosis. Also, Bingol et al³³ reported higher endocan levels in OSA patients than controls. Similarly, they could not find any difference for endocan levels between mild, moderate, or severe OSA.³³ In accordance with previous studies, we found higher endocan levels in stable COPD patients than controls. Endocan levels were not significantly different in COPD patients with different GOLD categories. Unlike ours and the other studies with stable lung diseases, the relationship between severity of disease and endocan has been shown in acute lung diseases. Güzel et al²⁸ reported that serum endocan levels can be considered a practical biomarker to determine the severity of pulmonary embolism. Kao et al²⁹ showed that high endocan values were associated with Pneumonia Severity Index, Confusion - Urea - Respiratory rate - Blood pressure (CURB-65), and Acute Physiology and Chronic Health Evaluation (APACHE II), which are the indicators of the disease severity. According to these results, we think that increased levels of endocan may represent a marker for severity of acute inflammatory lung diseases with endothelial dysfunction. Perhaps, endocan may not be a suitable biomarker for determining disease severity in stable lung diseases.

Except the study of Bingol et al,³³ none of the previous studies evaluated the relationship between endocan levels and hypoxemia. Bingol et al³³ showed no difference between endocan levels in OSA patients with and without nocturnal hypoxemia. Similarly, we did not find any difference between endocan levels in COPD patients with or without significant hypoxemia. Aciksari et al³⁴ excluded the patients with hypoxemia and impaired pulmonary tests while investigating the endothelial function in sarcoidosis.

Another feature of our study is that we analyzed the relationship between endocan and spirometric parameters. We found no correlation between endocan level and FEV₁ %.

COPD is often associated with comorbid conditions such as cardiovascular and cerebrovascular disease, osteoporosis, depression, lung cancer, and diabetes.^{37,38} All these comorbidities are characterized by systemic inflammation, and it has been hypothesized that chronic systemic inflammation

may be a key factor linking COPD and its comorbidities. So, it is accepted that comorbidities should be associated with increased systemic inflammation. Comorbidities such as hypertension and diabetes mellitus might be a reason for increased endocan levels in COPD. However, we could not find any difference between serum endocan levels of COPD patients with or without comorbidities. In addition, although comorbidities were similar in COPD and control groups, we found significantly higher endocan levels in patients with COPD than controls. Therefore, we cannot link high endocan levels to comorbidities in COPD patients. Similarly, Bingol et al³³ found that endocan levels were similar in OSA subjects with and without hypertension or diabetes mellitus. Also, comorbidities were similar in OSA patients and controls. Güzel et al²⁸ showed that endocan levels were not correlated with cardiac failure, hypertension, and pulmonary hypertension in patients with pulmonary thromboembolism.

One of the limitations of our study is the small sample size, but, this is the first study in the literature that has evaluated endocan levels in stable COPD. Another limitation is not evaluating inflammatory markers in our study. Most of the previous studies about endocan in lung diseases also did not evaluate inflammatory markers. Only Aciksari et al³⁴ investigated the correlation between serum endocan and C-reactive protein levels in patients with sarcoidosis, and they could not find any relationship between the two.

Conclusion

Serum endocan level was significantly higher in patients with stable COPD than controls. Further large-scale studies should be performed to explain the reason behind this mechanism.

Disclosure

The authors report no conflicts of interest in this work.

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