Kerman University of Medical Sciences and Health Services
Scientific Research Journal
Journal of Kerman University of Medical Sciences
JKMU
Journal of Kerman University of Medical Sciences, 2017; 24(3): 184-189

# The Relationship of Serum levels of Vascular Endothelial Growth Factor with Disease Severity and the Number of Exacerbations in COPD Patients

**Seyed-Mehdi Hashemi-Bajgani, M.D.[1], Mitra Samareh Fekri, M.D.[2], Hadi Zeydabadi, M.D.[3], Mohammad Rahmatian, M.Sc.[4], Arian Amirkhosravi, Ph.D.[5]**

1- Assistant Professor of Internal Medicine, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran
2- Associate Professor of Pulmonology, Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
3- General Practitioner, Afzalipour Hospital Research Center, Kerman University of Medical Sciences, Kerman, Iran
4- Master of Nursing, Vice-Chancellor for Curative Affairs, Kerman University of Medical Sciences, Kerman, Iran
5- Department of Pharmacology & Toxicology, School of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran (Corresponding author; E-mail: A.Amirkhosravi@kmu.ac.ir)

Received: 23 August, 2016 Accepted: 25 January, 2017

**ARTICLE INFO**

**Article type:**
Original article

**Keywords:**
Vascular Endothelial Growth Factor (VEGF)
COPD
Severity
Exacerbation

## Abstract

**Background:** Chronic Obstructive Pulmonary Disease (COPD) is a chronic lung disease characterized by progressive and irreversible obstruction of the airways of the lungs. Different studies have emphasized on the role of Vascular Endothelial Growth Factor (VEGF) in COPD patients. The aim of this study was to investigate the relationship of this factor with disease severity and the number of exacerbations in COPD patients.

**Methods:** This study is a Cross-sectional study on patients with chronic obstructive pulmonary disease referred to Besat clinic in Kerman in 2013-2014. After performing spirometery and confirming COPD diagnosis by a pulmonologist and obtaining consent form patients, blood samples were taken and level of VEGF was measured by ELISA method.

**Results:** Mean serum level of VEGF in patients was 160±156.6 µg/ml. More disease severity was associated with higher level of VEGF, but this association was not significant. No relationship was found between the number of exacerbations and VEGF level.

**Conclusion:** The results of our study showed that serum levels of VEGF increases in COPD patients, but there is not a significant correlation between serum levels of VEGF and the severity of the disease and the number of exacerbations.



**Citation:** Hashemi-Bajgani S.M, Samareh Fekri M, Zeydabadi H, Rahmatian M, Amirkhosravi A. The Relationship of Serum levels of Vascular Endothelial Growth Factor with Disease Severity and the Number of Exacerbations in COPD Patients. Journal of Kerman University of Medical Sciences, 2017; 24(3): 184-189.

## Introduction

Chronic obstructive pulmonary disease is a chronic lung disease characterized by progressive and irreversible obstruction of the respiratory tract. According to the GOLD criteria (Global Initiative for Obstructive Lung Disease), a person is diagnosed with COPD when his/her PFT (Pulmonary Function Test) or individual's lung function test (FEV1 / FVC) is less than be 70% (1). The most important risk factor for COPD is cigarette smoking. The common symptoms include exertion dyspnea, cough and Phlegm.

Vascular endothelial growth factor (VEGF) is a signal protein produced by vascular endothelial cells that stimulates angiogenesis. This protein is produced in response to hypoxia. The normal function of VEGF is formation of new blood vessels during embryonic development and after injury, angiogenesis for muscle after exercise, and the creation of collateral vessels after original vascular occlusion. Biological properties of VEGF in lung health and disease statues have led to an interest in its role (1, 2). In fact, studies have shown that VEGF expression in lung tissue obtained from patients with chronic obstructive airway disease has a major role in the pathology of the disease (3). In Kasahara et al. study, the expression of VEGF in sputum samples of patients with emphysema dropped. The authors demonstrated that the absence of VEGF, that is an important nutritional factor for endothelial cells, leads to the development of emphysema (3). Consistent with these findings, Pinto-Plata V found a positive relationship between VEGF concentration in the sputum sample and FEV1 in patients with stable COPD (4).

Due to the small number of studies about the relations of VEGF with COPD and absence of a study on the association of this factor with the number of exacerbations, this study was designed and done in order to investigate the relationship of serum levels of VEGF with the frequency and severity of COPD exacerbations.

## Methods

### Study population

This study was a cross-sectional study performed on patients with chronic obstructive pulmonary disease referred to Besat clinic in Kerman. The population consisted of 75 patients with COPD disease. Participants were selected by convenient sampling and the number of samples was determined according to the previous similar studies. Patients with the diagnosis of COPD confirmed by performing two-step spirometry were included and other patients with coagulation disorders, severe ventricular arrhythmia, heart/ liver / kidney failure and patients who had severe attacks (Exacerbation) were excluded. Then, the research objectives and all steps of the study and follow up were explained for all patients.

### Sampling

5 ml blood was drawn into EDTA tube and after centrifugation, stored at -70$_{o}$ C. Then, demographic data and number of exacerbations were recorded according to GOLD criteria and based on the result of spirometry in the previous year. Finally, VEGF level was measured using ELISA kits made in Germany (ZIGMA Company).

### Statistical analysis

To describe the qualitative variables, frequency tables and charts and for describing quantitative variables, mean ± SD were used. Data analysis was performed using chi-square test and t-test.

## Results

Of the 75 subjects enrolled in the study, 64 ones were male, and 12 ones were female.

As it is seen in figure 1, the disease severity was level 1 in 8 patients (10.5%), level 2 in 27 patients (5.35%), level 3 in 23 patients (3.30%) and level 4 in 18 patients (7/23%).

In this study, 32 patients (1.42%) did not have exacerbation, 16 patients (1.21%) had 1 exacerbation/per year, 8 patients (5.10%) had 2 exacerbations/per year, 8 ones (5.10%) had 3 exacerbations/per year and 12 patients (8.15%) had 4 or more exacerbations in the previous year (Fig. 2).

Mean serum level of VEGF was 160.45 ± 156.6 µg.

Mean serum VEGF level was 34.103 ± 11.244 µg in patients at the level 1 of GOLD criteria, 65.119 ±96.180 µg in patients at level 2, 38.213 ± 56.201 µg in patients at level 3, and 85.169 ± 63.217 µg in patients at level 4 (Fig. 3).

According the results, mean serum VEGF level was 53.19 ± 48.209 µg in patients with no exacerbation, 67.157 ± 34.233 µg in patients with one exacerbation/per year, 16.60 ± 8.136 µg in patients with two exacerbations /per year, 95.55 ± 62.94 µg in patients with three exacerbations /per year, and 93.194 ± 54.182 µg in patients with four exacerbations /per year.

The results of this study show that serum VEGF level has no significant relationship with the number of exacerbations and disease severity.

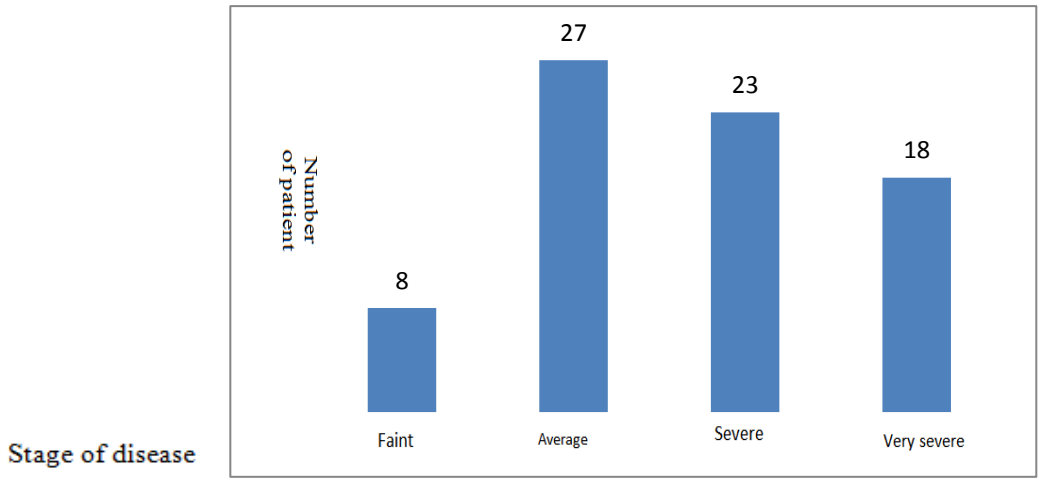


**Figure 1.** The frequency distribution of patients based on the disease severity

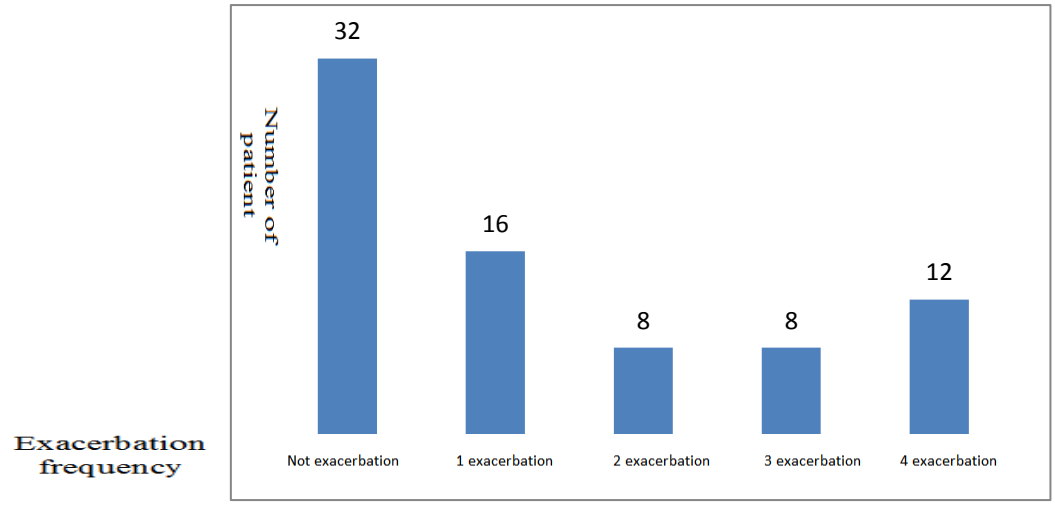


**Figure 2.** The frequency distribution of patients based on the number of exacerbations

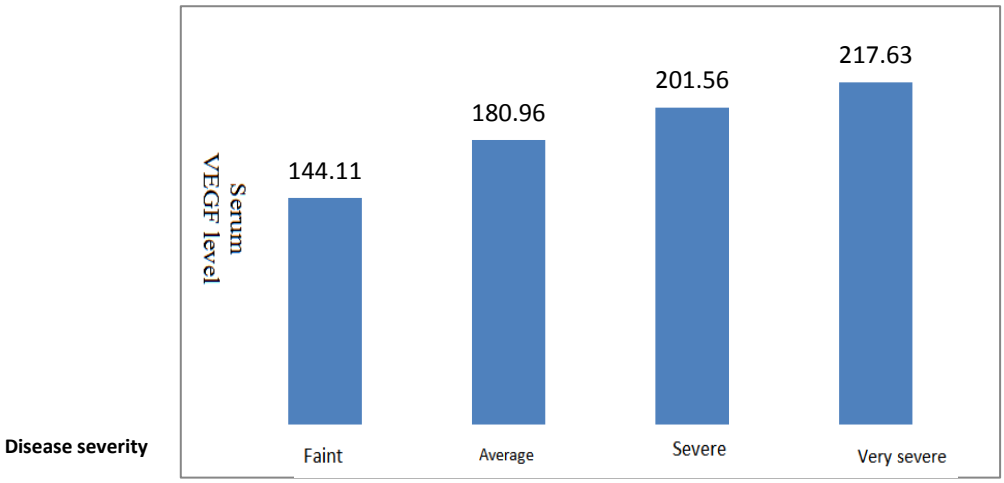


**Figure 3.** Serum VEGF levels based on the disease severity

## Discussion and Conclusion

The purpose of this study was to investigate the relationship of serum level of Vascular Endothelial Growth Factor (VEGF) with disease severity and number of exacerbations in COPD patients.

VEGF is a glycoprotein with six subtypes (A-F), which is known as the most important factor in angiogenesis, especially in the embryonic period (4, 5).

This cytokine plays a key role in epithelium and endothelium health and their protection against apoptosis. Over-expression of this factor in some diseases such as cancer causes angiogenesis increase in tumor tissue and consequently growth and proliferation of malignant cells due to better nutrition and oxygenation. Therefore, producing Anti- VEGF drugs, like Bevacizumab and Ranibizumab, for the treatment of cancer and other diseases that angiogenesis is involved in their pathogenesis (such as some vascular diseases of the retina) has been considered important (6).

The role of vascular injury in the pathogenesis of COPD is well known (6, 7). VEGF is involved in viability and remodeling of lung tissue, and the main drivers of its secretion are hypoxemia and increase of pulmonary arterial pressure (8, 9). Kranenburg et al., in the examination of samples of lung tissue in COPD patients compared with control group showed increased expression of VEGF in the bronchi, bronchioles, alveolar epithelium, bronchiolar macrophages and smooth muscle cells of the lung vessels and bronchi lining. As well, VEGF receptor-like KDR / FLK-1 and FLT-1 in pulmonary vascular endothelium of COPD patients was higher compared to non- COPD patients. Interestingly, they have reported an inverse relationship between the level of VEGF in lung tissue and FEV1 in patients with COPD (10). In the present study, mean serum level of vascular growth factor (VEGF) in patients with COPD was 16045 ± 156.6 µg/ml and the median was 122.66 µg/ml that are nearly compatible with Pinto-Plata et al. findings (4). The challenging issue is the relationship between VEGF level in serum and severity of the disease, because previous studies did not have similar results. In 2012 Pinto-Plata et al, failed to find the relationship between this factor serum level and disease severity (4). However, Pavlisa G and Kranenburg A compared VEGF level among patients with COPD, at time of exacerbation with hypoxemia (Po2≤53mmHg), stable COPD patients without hypoxemia and healthy people. They showed higher level of this factor in the first group compared to the other two groups (10, 11). Determining VEGF level at the time of the attack can be considered as one of the disadvantages of the mentioned study, because VEGF, as a cytokine, can be increased in any acute inflammation. Valipour et al studied 30 patients with stable COPD in 2008 and showed inverse relationship

between VEGF level in serum and FEV1; however, their study is not reliable due to their small sample size (12).

In our study, despite the fact that with increase of disease severity, serum levels of VEGF increased, the difference was not statistically significant. Although, the sample size of our study was higher than other studies, given that the disease severity in COPD patients falls into four groups, the reason of non-significant different VEGF levels in patients with different disease severity might be small number of samples in each group. It seems that there is a relation between hypoxemia and severity of COPD (13).

It is predicted that after FEV1 drop to less than 50 %, hypoxemia starts and after drop to less than 25%, the patient becomes gradually hypercapnic (14). With increase of disease severity, the number of COPD exacerbations increases. In our study, there was no significant relationship between the number of exacerbations and VEGF levels that might be due to small sample size. Studies with larger sample size that consider variables including the percentage of arterial oxygen pressure in the pulmonary artery at the same time and its association with vascular endothelial growth factor are recommended.

## References


1. Kaner RJ, Crystal RG. Compartmentalization of vascular endothelial growth factor to the epithelial surface of the human lung.*Molecular Medicine* 2001; 7(4):240-6.
2. Thickett DR, Armstrong L, Christie SJ, Millar AB.Vascular endothelial growth factor may contribute to increased vascular permeability in acute respiratory distress syndrome. *American journal of respiratory and critical care medicine*. 2001; 164(9):1601-5.
3. Kasahara Y, Tuder RM, Cool CD, Lynch DA, Flores SC, Voelkel NF. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema.American journal of respiratory and critical care medicine. 2001; 163(3):737-44.
4. Pinto-Plata V, Casanova C, Müllerova H, de Torres JP, Corado H, Varo N, et al. Inflammatory and repair serum biomarker pattern. Association to clinical outcomes in COPD. *Respiratory research* 2012; 13(1):71.
5. Cross MJ, Claesson-Welsh L. FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition. *Trends in pharmacological sciences* 2001; 22(4):201-7.
6. Wright JL, Lawson L, Paré PD, Hooper RO, Peretz DI, Nelems JB, et al. The Structure and Function of the Pulmonary Vasculature in Mild Chronic Obstructive Pulmonary Disease: The Effect of Oxygen and Exercise 1–3. *American Review of Respiratory Disease* 1983; 128(4):702-7.
7. Santos S, Peinado V, Ramirez J, Melgosa T, Roca J, Rodriguez-Roisin R, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD.*European respiratory journal* 2002; 19(4):632-8.
8. Voelkel NF, Cool C, Taraceviene-Stewart L, Geraci MW, Yeager M, Bull T, et al. Janus face of vascular endothelial growth factor: the obligatory survival factor for lung vascular endothelium controls precapillary artery remodeling in severe pulmonary hypertension. *Critical care medicine* 2002; 30(5):S251-S6.
9. Tuder RM, Flook BE, Voelkel NF. Increased gene expression for VEGF and the VEGF receptors

KDR/Flk and Flt in lungs exposed to acute or to chronic hypoxia. Modulation of gene expression by nitric oxide. *Journal of Clinical Investigation* 1995; 95(4):1798.

10. Kranenburg A, De Boer W, Alagappan VKT, Sterk P, Sharma H. Enhanced bronchial expression of vascular endothelial growth factor and receptors (Flk-1 and Flt-1) in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60(2):106-13.
11. Pavlisa G, Pavlisa G, Kusec V, Kolonic SO, Markovic AS, Jaksic B. Serum levels of VEGF and bFGF in hypoxic patients with exacerbated COPD. *European cytokine network* 2010; 21(2):8-92.
12. Valipour A, Schreder M, Wolzt M, Saliba S, Kapiotis S, Eickhoff P, et al. Circulating vascular endothelial growth factor and systemic inflammatory markers in patients with stable and exacerbated chronic obstructive pulmonary disease. *Clinical Science* 2008; 115:225-32.
13. Wright JL, Petty T, Thurlbeck WM. Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health nocturnal oxygen therapy trial. *Lung*. 1992; 70:109-24.
14. Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J. HARRISON'S Principles of Internal Medicine. Mc Graw Hill.19th edition. 2015; 1704-5.