Research Article / *Araştırma Makalesi*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2024; 63 (2): 215-222

Investigation of the morphometric structure of the retinal nerve fiber layer in patients with chronic obstructive pulmonary disease by optical coherence tomography

Kronik obstrüktif akciğer hastalığı olan hastalarda retina sinir lifi tabakasının morfometrik yapısının optik koherens tomografi ile incelenmesi

Sibel Ateşoğlu Karabaş[1], Aymelek Çetin[2], Gazi Gülbaş[3], Cem Çankaya[4], Deniz Şenol[5]

[1] Kahramanmaraş Sütçü İmam University Faculty of Medicine Department of Anatomy, Kahramanmaraş, Türkiye

[2] İnönü University Faculty of Medicine Department of Anatomy, Malatya, Türkiye

[3] İnönü University Faculty of Medicine Department of Chest Diseases, Malatya, Türkiye

[4] İnönü University Faculty of Medicine Department of Ophthalmology, Malatya, Türkiye

[5] Düzce University Faculty of Medicine Department of Anatomy, Düzce, Türkiye

ABSTRACT

Aim: To examine the changes in the retinal nerve fiber layer (RNFL) with Spectral-Domain Optical Coherence Tomography (SD-OCT) in individuals diagnosed with Chronic Obstructive Pulmonary Disease (COPD), according to Global Initiative For Chronic Obstructive Lung Disease (GOLD).

Materials and Methods: The study consisted of people 18 years or older, including 76 patients with COPD and 80 healthy control groups. Patients with COPD have been examined in four groups A, B, C and D, according to GOLD. RNFL thickness was examined through Optic Nerve Head (ONH) centered in four quadrants; superior, inferior, temporal, and nasal.

Results: In the Optic Nerve Head-centered peripapillary area, the RNFL thickness was observed to be thinner than control group in the inferior quadrant in GOLD B, GOLD C, and GOLD D groups compared to the control group (p=0.002). In the temporal quadrant, GOLD A and GOLD C groups were the thickest (p=0.001).

Conclusion: The patients with COPD included in our study were divided into groups by evaluating them according to the updated GOLD criteria and we think that this aspect has contribution to the literature. It has been observed that COPD causes changes in the RNFL, especially in its later stages. It would be appropriate to consult in terms of eye diseases for the evaluation of retinal functions in COPD patients.

Keywords: Morphometry, chronic obstructive pulmoner disease, Spectral-Domain Optical Coherence Tomography, retinal nerve fiber layer.

NOTE: *The study has been presented at the "II. Internatıonal Battalgazi Scıentıfıc Studies Congress" between March 15-17, 2019.*

ÖZ

Amaç*: Global İnitiative For Chronic Obstructive Lung Disease (GOLD)'a göre Kronik Obstrüktif Akciğer Hastalığı (KOAH) tanısı alan bireylerde retina sinir lifi tabakası (RSLT)'nda oluşan değişimlerin Spektral Domain-Optik Koherans Tomografi (SD-OKT) ile incelenmesi amaçlanmaktadır.*

Corresponding author: Sibel Ateşoğlu Karabaş
Kahramanmaraş Sütçü İmam University Faculty of Medicine
Department of Anatomy, Kahramanmaraş, Türkiye
E-mail: *sibelatesoglu@gmail.com*
Application date: 03.04.2023 Accepted: 31.10.2023

Gereç ve Yöntem: *Çalışmaya 18 yaş ve üstü 76 KOAH'lı, 80 sağlıklı birey dahil edilmiştir. KOAH'lı hastalar GOLD'a göre tanı konularak A, B, C ve D olmak üzere dört grupta incelenmiştir. RSLT kalınlıkları optik sinir başı (OSB) merkezli superior, inferior, temporal ve nazal olmak üzere dört kadranda incelenmiştir.*

Bulgular: *OSB merkezli peripapillar alanda RSLT kalınlığının; inferior kadranda GOLD B, GOLD C ve GOLD D gruplarında kontrol grubuna göre daha ince (p=0.002), temporal kadranda ise GOLD A ve GOLD C gruplarında en kalın olduğu tesbit edilmştir (p=0.001).*

Sonuçlar: *Çalışmamıza dâhil edilen KOAH'lı hastalar güncellenen GOLD kriterlerine göre değerlendirilerek gruplara ayrılmıştır ve bu yönüyle literatüre zenginlik katmış olduğunu düşünmekteyiz. KOAH'ın özellikle ilerleyen evrelerinde RSLT'nda değişikliklere yol açtığı görülmüştür. KOAH'lıların retinal fonksiyonlarının değerlendirilmesi için göz hastalıkları açısından konsülte edilmesi uygun olacaktır.*

Anahtar Sözcükler*: Morfometri, kronik obstruktif akciğer hastalığı, Spektral Domain-Optik Koherans Tomografi, retina sinir lifi tabakası.*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease condition caused by the body's abnormal inflammatory response to small particles or certain gases that can damage the airways, leading to progressive airway narrowing and irreversible airflow limitation (1). Inflammation in COPD is usually caused by exposure to harmful substances such as cigarette smoke. These inhaled irritants cause vascular endothelial cells and circulating leukocytes to become active. Platelets and leukocytes released by the bone marrow initiate the release of C-reactive protein (CRP, interleukins and fibrinogen) and thus inflammation. In addition to triggering the production of inflammatory mediators, they also cause tissue damage (2).

Retinal nerve fiber layer (RNFL) and choroid layers are complex microvascular systems that can be easily affected by systemic diseases such as COPD (3). It has been proven by studies that COPD also causes a decrease in RNFL and ganglion cell layer (GCL) thickness (4). There are studies showing that endothelin-1 (ET-1), a vasoconstrictor that causes systemic vascular effects due to oxidative stress, is increased in both plasma and urine of patients with COPD (5). It has been found that high resistance is seen in many orbital arteries due to the increase in ET-1 enzymes in COPD (6). Such disturbances in hemodynamic blood circulation in the fundus lead to decreased perfusion of the optic nerve head (ONH) and loss of ganglion cells in the retina (7). Normal choroidal vasculature is necessary for the retina to function. Decreased thickness of the choroidal layer or loss of vascular structures also cause damage in photoreceptors (4). High-resolution spectral domain optical coherence tomography (SD-OCT), which provides noninvasive visualization of the retrobulbar hemodynamics of COPD and its clinical effects on retinal layers, is an indispensable imaging method used in clinics (8).

It should be kept in mind that all structures in the eye may be affected in hypoxia and systemic inflammation occurring in COPD (9). There have been several studies showing a reduction in RNFL thickness in COPD, but controversial results have been obtained. As far as we know, there are a limited number of studies examining COPD in four stages according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and evaluating RNFL with SD-OCT. In this study, we aimed to reveal the possible effects of the disease on RNFL by dividing COPD into four groups according to GOLD and examining the thickness of the RNLF with SD-OCT.

MATERIALS and METHODS

Participants were asked to sign a volunteer form indicating their acceptance of the study. The study was conducted in accordance with the Declaration of Helsinki.

Participants and Study Design

Patients diagnosed according to GOLD were divided into four groups as GOLD A, GOLD B, GOLD C, and GOLD D, and the total sample number was calculated as 76, with 19 patients in each group. Measurements were taken from both eyes of the patients, and a total of 152 eyes from the patient group were studied. The control group was determined as 80 individuals and

measurements were taken from both eyes, resulting in a total of 160 eyes included in the control group.

Spirometry tests

Participants were selected from patients who came to the chest diseases outpatient clinic for routine examinations and were diagnosed with COPD. Routine examinations such as anamnesis, physical examination findings, spirometry, pulmonary function tests, number of symptoms/exacerbations are performed to patients who come to the chest diseases outpatient clinic, and their stage of COPD was determined as GOLD A, GOLD B, GOLD C, and GOLD D according to GOLD by the physician. As a result of spirometry measurements, the grouping of patients according to airflow limitation is demonstrated in Table-1 (Table-1).

Ophthalmic examination

Patients included in the study were directed to the ophthalmology clinic and a comprehensive ophthalmologic examination was performed by the same ophthalmologist. Assessment of the anterior segment structures with biomicroscope, refractive error (RE), axial length (AL), intraocular pressure best-corrected visual acuity (BCVA), measurement, and a detailed fundus examination was performed. We included subjects with AL≤24 mm, BCVA≥8/10, an open angle evident on gonioscopy, RE≤±3.0 diopters, a cup-to-disc ratio≤0.3 in each eye, cup-to-disc ratio asymmetry ≤0.2, intraocular pressure ≤21 mm Hg. Cases resulting in no ocular and systemic disease were eligible for the study. Patients with ocular pathologies such as macular degeneration, history of ocular surgery, ocular hypertension, uveal and ocular inflammation, eye trauma, amblyopia, optic neuropathy, cardiovascular diseases and diabetes mellitus were excluded.

SD-OCT

Retinal images were taken with OCT from patients approved for the study. In RNFL thickness examinations, all measurements were made with SD-OKT (NIDEK RS-3000, Aichi, Japan) device and Heidelberg Engineering OCT-Spectral device. During the measurement, the patient's head was kept upright and in the same posture. The best of the measurements are recorded for analysis, provided that the signal strength is not less than 7. No medication or invasive administration was performed to the patients for retinal measurements. To measure peripapillary RNFL thickness, optic disc cube scan protocol (200 × 200 pixels) images were recorded in a 6x6mm2 area with optic disc center. RNFL thickness was examined through Optic Nerve Head (ONH) centered in four quadrants; superior, inferior, temporal, and nasal. Other data obtained from the patients included oxygen saturation by pulse oximetry, gender, age, their height in centimeters, their weight in kilograms and body mass index (BMI) calculation.

Statistical Analysis

For statistical analysis of the data, IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA) package program was used. To compare the groups, the Kruskal-Wallis test and the Conover binary comparison method were used respectively. These data are summarized as median, minimum, and maximum values. In evaluating the level of significance in the analysis, a P-value equal to and less than 0.05 was considered statistically significant.

RESULTS

The ages of the individuals in the GOLD A group were found to be significantly younger compared to other COPD groups (p=0.001). There was no significant difference between the control group and the GOLD groups in terms of BMI (p=0.147). Oxygen saturation was found to be the highest in the GOLD A and the lowest in the GOLD D group (p=0.001) (Table-2). 84.2% of the GOLD A group were male, 15.8% female; 94.7% of the GOLD B group were male, 5.3% female; 73.7% of the GOLD C group were male, 26.3% female; 94.7% of the GOLD D group were male 5.3% of them were female.

ONH-centered RNFL thickness measurements in the superior and nasal quadrants were not different between the GOLD groups and the control group (p, 0.098 and 0.073, respectively); in the inferior quadrant, GOLD B, C, and D groups were thinner than the control group and there was no difference in GOLD A (p = 0.002); and in the temporal quadrant, it was observed the thickest in GOLD A and C groups (p = 0.001) (Table-3, Figure-1).

Table-1. Global Initiative For Chronic Obstructive Lung Disease (GOLD) Chronic Obstructive Pulmonary Disease (COPD) Classification.

COPD Stages	COPD Severity	Respiratory Function Test Values	
		Postbronchadilator FEV1/FVC	FEV 1(% predicted)
GOLD A	Mild	< 0.7	FEV1 ≥ 80
GOLD B	Moderate	< 0.7	50 ≤ FEV1 < 80
GOLD C	Severe	< 0.7	30 ≤ FEV1 < 50
GOLD D	Very Severe	< 0.7	FEV1 < 30or< 50 and chronic respiratory failure

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; GOLD A, Mild Chronic Obstructive Pulmonary Disease; GOLD B, Moderate Chronic Obstructive Pulmonary Disease; GOLD C, Severe Chronic Obstructive Pulmonary Disease; GOLD D, Very Severe Chronic Obstructive Pulmonary Disease; FEV1, Volume of air exhaled in one second of forced expiration, FVC, Forced vital capacity.

Table-2. Demographic properties and oxygen saturation of groups.

Variable	Control Group	GOLD A Group	GOLD B Group	GOLD C Group	GOLD D Group	p
Age (Year) Means ± SD (Min-Max)	51.01±13.03 (22-85) [a]	55.11±13.96 (30-79) [a]	64.37±9.25 (46-81) [b]	63.16±8.81 (39-86) [b]	65.47±8.63 (50-81) [b]	0.001
BMI(kg/m²) Means ± SD (Min-Max)	26.13±3.55 (20-38)	26.32±4.47 (19-36)	24.37±2.85 (20-31)	24.47±4.89 (18-34)	23.74±3.98 (25-16)	0.147
Oxygen saturation(%) Means ± SD (Min-Max)	96.42±1.66 (92-99) [a]	95.84±1.89 (93-98) [a]	92.68±3.46 (85-98) [b]	93.32±2.31 (88-96) [b,c]	89.37±6.27 (70-96) [c]	0.001

Abbreviations: BMI, Body mass index, GOLD A, Mild Chronic Obstructive Pulmonary Disease; GOLD B, Moderate Chronic Obstructive Pulmonary Disease; GOLD C, Severe Chronic Obstructive Pulmonary Disease; GOLD D, Very Severe Chronic Obstructive Pulmonary Disease.(a,b,c: It shows the significant difference (p <0.05) among the means indicated by different letters (a-b-c) in the same line).

Table-3. Retinal nerve fiber layer thickness measurements of groups in four quadrants from discus nervi optici.

ONH from RNFL c(µm)	Conrol Group	GOLD A Group	GOLD B Group	GOLD C Group	GOLD D Group	p
Superior	135 (28-350)	131.5 (55-320)	119 (50-330)	125.5 (102-404)	127.5 (45-577)	0.098
Inferior	135 (0-654) [a,c]	141 (46-491) [a]	118.5 (39-185) [b]	132 (77-410) [b,c]	129.5 (49-900) [b,c]	0.002
Temporal	71.5 (23-631) [a]	80 (47-335) [b,c]	68 (43-189) [a,b]	84 (38-805) [c]	69 (0-527) [a]	0.001
Nasal	80 (34-721)	96.5 (53-276)	84 (30-185)	91.5 (33-470)	84.5 (25-875)	0.073

Abbreviations: ONH, Optic nerve head; RNFL, Retinal nerve fiber layer; µm, micrometer; GOLD A, Mild Chronic Obstructive Pulmonary Disease; GOLD B, Moderate Chronic Obstructive Pulmonary Disease; GOLD C, Severe Chronic Obstructive Pulmonary Disease; GOLD D, Very Severe Chronic Obstructive Pulmonary Disease. (a,b,c: It shows the significant difference (p <0.05) among the means indicated by different letters (a-b-c) in the same line).

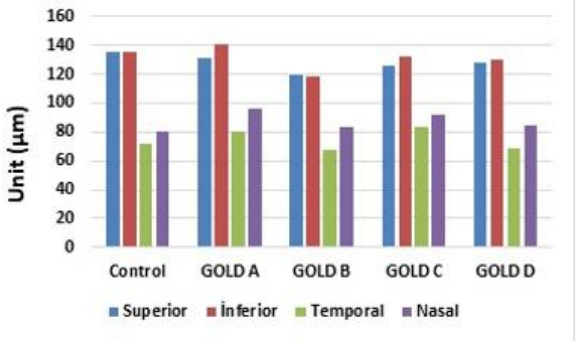

Figure-1. Retinal nerve fiber layer thickness measurements in the peripapillary area.

DISCUSSION

COPD is a chronic disease increasing in prevalence, and causing serious consequences in physical, mental, and social aspects (10). Especially in developing countries, COPD and COPD related deaths are higher in males than in females (11).

In studies investigating the frequency of COPD and gender correlation, a male predominance is reported. Among 62 patients with COPD, 51 were males and 11 were females in a study performed by Wegner et al. (12). Postma et al. reported that 81% of the patients were male and 19% were female (13). When we look at the studies conducted in Turkey, it has been determined that COPD is more common in men than in women (14). Similar to the studies conducted, also in our study it was observed that COPD was more common in male individuals in all GOLD groups. We can explain this situation in the underdeveloped and developing countries by the fact that smoking habit and amount of use is higher in men than in women. In addition to this, we can say that occupational exposure is higher in men than women because men work more than women in places that require more muscle strength such as mines and factories.

COPD not only affects the lungs but also brings many systemic disorders such as nutritional deficiency, malnutrition, skeletal-muscle dysfunction, cardiovascular, endocrinological, and neurological effects (10). For this reason, dietary habits of those diagnosed with COPD also gain importance. Our results show that there is no difference between the healthy individuals and COPD groups in terms of BMI. In the research by Özçimen et al. on patients with COPD, the BMI of the patient group was found 22.90 ± 1.75 kg/m², the control group was found 22.30 ± 1.81 kg/m² and demonstrated no statistically significant difference (4). Our BMI results were in parallel with the results of Özçimen et al.

Over time, COPD may affect all systems in our body, leading to some changes in metabolism, some structural disruptions in the respiratory muscles, and consequently hypoxia and hypercapnia, decreased ventilation in the alveoli and thus decreased arterial oxygen saturation (15). Özçimen et al. detected that the oxygen saturation measured by pulse oximetry was 87.00 ± 8.70% in COPD patients and 91.21 ± 4.35% in the control group. It is suggested that resulting hypoxia causes ganglion cell death and decreased RNFL thickness in COPD patients (4). Also, Pesci et al. obtained partial oxygen pressure as 70.8 mmHg in COPD patients and 95.5 mmHg in the control group (2). Salepçi et al. reported oxygen saturation (SaO2) as 92.20 ± 3.83% in patients with COPD (16). Özer et al. measured the oxygen saturation with pulse oximetry and found 96.8 ± 0.5% in patients with the I.group mild COPD; 94.1 ± 1.4% in II. group with moderate COPD; 90.0 ± 2.7% in III. group with severe COPD and 97.3 ± 0.9% in the control group (6). In our study, oxygen saturation was highest in the control group and lowest in the severe GOLD D group, similar to study by Özer et al. The results of our study are consistent with all of these studies, and it is revealed that oxygen saturation is lower in individuals with COPD compared to the control group.

It has been proven by studies that COPD causes a decrease in RNFL and GCL thickness (4). In our study, RNFL thickness in the peripapillary area was found to be statistically significantly thinner in the inferior quadrant in the GOLD B, C and D groups compared to the control group. Ghee et al. found that there was no difference between the GOLD 1 and GOLD 2 groups in the inferior quadrant with the control group, but there was a statistically decrease in GOLD 3 and GOLD 4 (17). Our results are in great agreement with this study, but in our study, there was a decrease in the GOLD B as well. Similar to our results, a study showed that RNFL thickness in the inferior quadrant was thinner in the COPD group compared to the healthy individuals. They suggest that this decrease is due to systemic inflammation and hypoxia (18). We also think that there is a decrease in RNFL in the inferior quadrant due to hypoxia due to the inability to

provide effective ventilation in COPD. Hypoxia and inflammation caused by COPD, which is a chronic systemic disease, lead to the emergence of certain substances that are indicators of oxidative stress and may disrupt the balance between oxidant-antioxidant (19). This causes the nerves in the axons and the cells in the ganglia to be destroyed (20). The retina layer, which has a very fast metabolic activity, naturally consumes oxygen quite rapidly. In the later stages of COPD, hypoxemia occurs due to the effect of the gas exchange unit of the lungs, while hypercapnia develops due to the effect of ventilation. We believe that this situation may lead to impaired metabolism in the retina layer and a decrease in its thickness. Again, we think that the higher impact in the inferior quadrant in the GOLD B, C and D groups may be due to the higher mean age of these groups compared to the GOLD A and control groups. In healthy individuals, endothelial tissue maintains an important balance between substances vasoconstrictive effects such as thromboxane, prostaglandin H, ET-1 originating from the endothelium and nitric oxide, which is a vasodilator (21). In particular, nitric oxide and ET-1 are responsible for maintaining blood flow in the eye and tone in arterioles (22). In COPD patients, have shown an increase in serum and urine ET-1 levels due to endothelial dysfunction (5,23). Endothelial dysfunction in COPD patients is thought to be caused by oxidative stress due to widespread smoking, persistent hypoxia and circulating inflammatory cytokines (24). It is widely believed that ET-1 levels in plasma, especially when persistent hypoxia occurs, increase blood flow resistance in the arteries of the eye through vasospasm and affect the retinal vessels (21,25). This situation suggests that it causes RNFL thinning. Alim et al. reported that the inferior quadrant was decreased in the COPD group compared to the healthy group, but the difference was not significant (26). Gok et al. did not find a difference in the inferior quadrant of COPD patients compared to the healthy group, and they also stated that there was no difference between the GOLD groups (27). Turan et al. stated that they did not detect a statistical difference in the inferior quadrant in their study in patients with advanced COPD (28). These results are similar to the results of the GOLD A group in our study.

In our results, it was observed that RNFL thickness in the superior quadrant decreased in GOLD A, B, C and D groups compared to the healthy group, but the difference was not significant. In Uğurlu et al. studies, a decrease was detected in the superior quadrant similar to our findings, however, it was observed that there was no statistical difference (18). In Alim et al. study, similar to our results, they stated that the superior quadrant decreased in the COPD group compared to the healthy group, however, this difference was not significant (26). Gok et al. stated in their study that the superior quadrant did not change in COPD patients compared to the healthy group, and at the same time, there was no statistical difference between the GOLD1, 2 and GOLD 3, 4 groups compared to the healthy individuals, similar to our findings (27). In a study, contrary to our results, it was stated that there was a significant decrease in the superior quadrant of the GOLD 1, 2, 3 and 4 groups compared to the control group (17). In a research conducted in patients with third and fourth stage COPD, contrary to our results, it was found that RNFL thickness was higher in the superior quadrant when compared to the healthy individuals (28). When the results of the studies in the literature are evaluated, the results regarding the RNFL thickness of individuals differ. We think that these differences might be due to the selection of patients examined, the number of samples, gender ratios, differences in mean ages, and different measurement methods used.

In our results, it was found that RNFL thickness in the nasal quadrant reduced in COPD groups compared to healthy subjects, but this decrease was not significant. Similar to our results, a decrease in the nasal quadrant was detected in the different studies performed, but it was determined that there was no statistical difference (18,26-28). Similar to our study, the results of Ghee et al. showed that there was no decrease in GOLD 1 only. They determined that there was a significant decrease in the nasal quadrant in the GOLD 2, 3 and 4 groups. They also stated that there is a strong relationship between the severity of COPD and RNFL thickness, and that as the GOLD stage increases, the increased resistance in the peripheral airway compromises ocular blood flow and causes a decrease in RNFL thickness (17).

In our study, it was concluded that RNFL thickening in the temporal quadrant was observed in the GOLD A and C groups compared to the healthy individuals. The difference was

found to be significant. In the research conducted by Turan et al. in individuals with third and fourth stage COPD, it was found that RNFL thickness in the peripapillary area was higher in the temporal quadrant compared to healthy individuals (28). Similar to this study, in the temporal quadrant in our study, it was determined that there was thickening in the severe stage GOLD C group compared to the others. Contrary to our results in other studies, a decrease was found in the temporal quadrant, but the difference was not significant (18, 26, 27). In another study, contrary to our results, it was determined that there was a decrease in all four GOLD groups compared to the healthy group (17). Studies in the literature it has been suggested that migraine attacks and changes in retinal or ONH microcirculation may cause hypoperfusion in migraine patients (29,30). Likewise, if COPD is not controlled, it causes many complications such as pulmonary insufficiency, tricuspid insufficiency, secondary pulmonary hypertension, respiratory insufficiency, cyanosis, lung cancer, and hypoxemia (4).We believe that these complications may lead to decrease in RNFL thickness and visual impairments in the long term by causing hypoperfusion in the retinal layer.

The limited sample size and the fact that the majority of the participants were male individuals constitute a limitation of this study. As the weakness of the study, it would be appropriate to explain that the age distribution between the groups is not similar. Although there are a few studies in the literature that reveal RNFL thickness in COPD cases, the number of studies is still inadequate. Further research should be undertaken to investigate this subject.

CONCLUSION

We believe that RNFL thickness can be useful for our physicians in determining the possible effects of COPD on the retina and clinical evaluation of the patient. The patients with COPD included in our study were divided into groups by evaluating them according to the updated GOLD criteria and we think that this aspect has added richness to the literature. According to our findings, it was determined that COPD affects RNFL. As a result, it would be appropriate to consult the eye diseases department in terms of retinal functions in patients with COPD.

Conflict of interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: I would like to thank the İnönü University Scientific Research Projects Coordination Unit which supports this study. (ID:771 Project number: TDK-2018-771).

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. Am J Respir Crit Car Med. 2017; 195: 557-82.
2. Pesci A, Balbi B, Majori M, et al. Inflammatory cells and mediators in bronchial lavage of patients with chronic obstructive pulmonary disease. Eur Respir J 1998; 12(2): 380–6.
3. Xin C, Wang J, Zhang W,et al. Retinal and choroidal thickness evaluation by SD-OCT in adults with obstructive sleep apnea-hypopnea syndrome (OSAS). Eye 2014; 28(4): 415–21.
4. Özçimen M, Sakarya Y, Kurtipek E, et al. Peripapillary choroidal thickness in patients with chronic obstructive pulmonary disease. Cutan Ocul Toxicol 2016; 35: 26-30.
5. Roland M, Bhowmik A, Sapsford RJ, et al. Sputum and plasma endothelin-1 levels in exacerbations of chronic obstructive pulmonary disease. Thorax 2001; 56: 30–5.
6. Ozer T, Altin R, Ugurbas SH, et al. Color Doppler evaluation of the ocular arterial flow changes in chronic obstructive pulmonary disease. Eur J Radiol 2006; 57(1): 63-8.
7. Yanagi M, Kawasaki R, Wang JJ, et al. Vascular risk factors in glaucoma: a review. Clin Experiment Ophthalmol 2011; 39(3): 252-8.
8. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 2008; 146: 496–500.
9. Adhi M, Duker JS. Optical coherence tomography-current and future applications. Curr Opin Ophthalmol 2013; 24(3): 213–21.
10. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009; 33: 1165-85.
11. Mannino DM, Homa DM, Akinbami LJ, et al. Chronic obstructive pulmonary disease surveillance – United States, 1971–2000. MMWR Surveill Summaries 2002; 51: 1–16.

12. Korkut S. Evaluation of patients with depression which come with chronic obstructive pulmonary disease (COPD) attack to the emergency medicine. Faculty of Medicine Department of Chest Diseases [Master thesis], Düzce, Düzce Universty, 2012.
13. Kara M, Mirici A. Loneliness, depression, and social support of Turkish patients with chronic obstructive pulmonary disease and their spouses. J Nurs Scholarsh 2004; 36: 331-6.
14. Türkkan S. Prevelance of cronıc obstuctive pulmonary disease ın fırst degree relatives of COPD patients, Faculty of Medicine Department of Chest Diseases. İ.Ü [Master thesis], 2012.
15. Congleton J. The pulmonary cachexia syndrome; aspects of energy balance. Proc Nutr Soc 1999; 58: 321-8.
16. Salepçi B, Eren A, Çağlayan B, et al. The effect of body mass index on functional parameters and quality of life in COPD patients. Tüberculosis and Thorax 2007; 55(4): 342-9.
17. Ghee1 YT, Mustapha1 M, Harun R, et al. Retinal nerve fiber layer thickness in chronic obstructive pulmonary disease: An optical coherence tomography study. Asian J Ophthalmol 2017; 15: 151-8.
18. Ugurlu E, Pekel G, Altinisik G, et al. New aspect for systemic effects of COPD: eye findings. Clin Respir J 2018; 12:247–52.
19. Domej W, Oettl K, Renner W. Oxidative stress and free radicals in COPD– implications and relevance for treatment. Int J Chron Obstruct Pulmon Dis 2014; 9(1): 1207–24.
20. Palombi K, Renard E, Levy P, et al. Non-arteritic anterior ischaemic optic neuropathy is nearly systematically associated with obstructive sleep apnoea. Br J Ophthalmol. 2006; 90(7): 879–82.
21. Polak K, Luksch A, Frank B, et al. Regulation of human retinal blood flow by endothelin-1. Exp Eye Res 2003; 76: 633–40.
22. Donati G, Pournaras CJ, Munoz JL, et al. Nitric oxide controls arteriolar tone in the retina of the miniature pig. Invest Ophthalmol Vis Sci. 1995; 36: 2228–37.
23. Sofia M, Mormile M, Faraone S, et al. Increased 24-h endothelin-1 urinary excretion in patients with chronic obstructive pulmonary disease. Respiration 1994; 61:263–8.
24. Agusti A, Soriano JB. COPD as a systemic disease. Chronic Obstr Pulm Dis 2008; 5: 133–8.
25. Nikolaou E, Trakada G, Prodromakis E, et al. Evaluation of arterial endothelin-1 levels, before and during a sleep study, in patients with bronchial asthma and chronic obstructive pulmonary disease. Respiration 2003; 70(6): 606–10.
26. Alim S, Demir HD, Yilmaz A, et al. To evaluate the effect of chronic obstructive pulmonary disease on retinal and choroidal thicknesses measured by optical coherence tomography. J Ophthalmol 2019; Oct:1-5.
27. Gok M, Ozer MA, B, Ozen S, et al. The evaluation of retinal and choroidal structural changes by optical coherence tomography in patients with chronic obstructive pulmonary disease. Curr Eye Res 2018; 43(1): 116–21.
28. Turan M. The evaluation of retinal nerve fiber layer thickness by optical coherence tomography in patients with chronic obstructive pulmonary disease. Faculty of Medicine Department of Ophthalmology [Master thesis], Konya, Selcuk University, 2009.
29. Martinez A, Proupim N, Sanchez M. Retinal nerve fibre layer thickness measurements using optical coherence tomography in migraine patients. Br J Ophthalmol 2008; 92: 1069-75.
30. Kırbas S, Tufekci A, Turkyilmaz K, et al. Evaluation of the retinal changes in patients with chronic migraine. Acta Neurol Belg 2013; 113(2): 167-72.