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The Evaluation of Retinal Nerve Fiber Layer Thickness by Optical Coherence Tomography in Patients with Chronic Obstructive Pulmonary Disease

Kronik Obstrüktif Akciğer Hastalığı Olan Olgularda Retina Sinir Lifi Kalınlığının Optik Koherens Tomografi ile Değerlendirilmesi

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Öz

Amaç: Kronik obstrüktif akciğer hastalığı (KOAH) olan hastalarda retina sinir lifi tabakası (RNFL) ve optik sinir başı (ONH) değişikliklerini değerlendirmeyi amaçladık.
Hastalar ve Yöntem: Çalışmaya ağır KOAH'lı 30 hasta ve yaş ve cinsiyet açısından eşleştirilmiş 29 sağlıklı kişi alındı. Ayrıntılı bir oftalmik muayeneden sonra, ONH ve RNFL kalınlık ölçümleri optik koherens tomografi (OCT) (Stratus OCT-3) ile yapıldı. Arteriyel kan gazları (pO_2 ve PCO_2) ölçüldü ve KOAH hastalarının evrelemesi için solunum fonksiyon testleri yapıldı. OCT parametreleri, bağımsız t testi kullanılarak iki grup arasındaki fark karşılaştırılırken, solunum fonksiyon testleri, arter kan gazı ve RNFL kalınlık parametreleri arasındaki korelasyonu değerlendirmek için Pearson korelasyon analizi yapıldı. P değerinin 0.05'ten küçük olması istatistiksel olarak anlamlı kabul edildi.
Bulgular: KOAH ile sağlıklı bireyler arasında optik disk alanı, kap alanı ve rim alanı açısından anlamlı fark yoktu (p> 0,05). KOAH hastalarında ortalama ve üst kadran RNFL kalınlık parametrelerinin kontrol grubuna (sırasıyla 107.9 ± 5.4 µm ve 131.31 ± 13.6 µm) göre anlamlı derecede daha kalın olduğu (sırasıyla 114.52 ± 7.7 µm ve 141.07 ± 18.2 µm) p= <0.05) bulundu. PO_2 ve RSLT kalınlığı arasında anlamlı korelasyon saptanmadı (r = -0.22, p = 0.33), pCO_2 ve üst kadran RNFL arasında orta derecede anlamlı korelasyon bulundu (r = 0.53 ve p = 0.017) ve FEV1 / FVC ve üst kadran RNFL arasında yüksek negatif yönlü korelasyon bulundu. (r = -0.76, p = 0.003).
Sonuç: pCO_2'deki artış ve FEV1 / FVC'deki azalma, artmış hipoksiyi göstermektedir. RGC ölümüyle ilişkili olan peripapiller RNFL kaybını hipoksi / iskemi kaynaklı retina ve optik disk ödemi tarafından maskelenebilir. KOAH hastalarında ortalama RNFL kalınlığındaki artışın, artmış hipoksi ile ilişkili retinal ödeme bağlı olduğu düşünüldü.

Anahtar Kelimeler: Kronik obstrüktif akciğer hastalığı, retina sinir lifi kalınlığı, Optik koherens tomografi

Abstract

Aim: We aimed to assess the changes in retinal nerve fiber layer (RNFL) and optic nerve head (ONH) in patients with chronic obstructive pulmonary disease (COPD).
Patients and Methods: Thirty patients having severe COPD and 29 age and sex-matched healthy subjects were enrolled in the study. After a detailed ophthalmic examination, the ONH and RNFL thickness measurements were taken by an optical coherence tomography (OCT) (Stratus OCT-3). Arterial blood gases (pO_2 and PCO_2) were measured and respiratory functional tests were performed for the staging of COPD patients. The OCT parameters were compared difference between the 2 groups using independent t test, while Pearson correlation analysis was performed to assess the correlations between respiratory functional tests, arterial blood gases and RNFL thickness parameters. A p value less than 0.05 was accepted as statistically significant.
Results: There were no significant differences in optic disc area, cup area and rim area between COPD and healthy subjects (p>0.05). Parameters of mean and superior quadrant RNFL thickness were found to be significantly thicker in COPD subjects (114.52±7.7 µm and 141.07 ±18.2 µm, respectively) compared to the control subjects (107.9±5.4 µm and 131.31±13.6 µm, respectively) (p<0.05). No correlation was found between pO_2 and RNFL thickness (r=-0.22, p=0.33). There was a moderate correlation between pCO_2 and superior quadrant RNFL (r= 0.53 and p=0.017), and a high negative correlation between FEV1/FVC and superior quadrant RNFL (r=-0.76, p=0.003).
Conclusions: The increase in pCO_2 and the decrease in FEV1 / FVC indicate increased hypoxia. Peripapillary RNFL loss associated with RGC death can be masked by hypoxia / ischemia-induced retinal and optic disc edema. Increased mean RNFL thickness in COPD patients was thought to be due to retinal edema associated with increased hypoxia.

Key words: Chronic obstructive pulmonary disease, Retinal nerve fiber layer thickness, Optical coherence tomography

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a group of lung diseases characterized by airflow obstruction with breathing-related symptoms such as chronic cough, expectoration, exertional dyspnea, and wheeze (1-2). COPD is most commonly associated with chronic bronchitis, emphysema and a subset of patients with asthma. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) described COPD as "a disease state characterized by progressive airflow limitation that is not fully reversible and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases'' (3). The best known risk factor for the development of COPD is tobacco smoking. Emerging evidence suggests that air pollution, occupational exposure to dusts and gases, infections, chronic asthma, and genetic factors may also play role in the pathogenesis, especially in developing countries. COPD is a systemic disease with increased risk of atherosclerosis, cardiovascular disease and polyneuropathy (4-9). Reduced gas exchange capacity of the lungs with hypoxemia, co-associated atherosclerosis, smoking, increased oxidative stress, inflammatory cytokines and ageing all contribute to local hypoxia/ischemia in COPD.

Retina, being one of the most metabolically active tissues in the body, consumes an enormous amount of oxygen for the conversion of light to an electrical signal by the photoreceptors (10-12). Therefore it needs constant oxygen supply to establish its structural and functional integrity. It has a dual circulation; the photoreceptors and outer plexiform layer of the retina is supplied by choriocapillaris, while superficial and deep capillary plexuses formed by the branches of retinal central artery supplies the inner retinal layers (13). Retinal hypoxia is a mechanism underlying many sight-threatening disorders such as ischemic retinal vein thrombosis, central retinal artery occlusion, some types of glaucoma, and diabetic eye disease complications (14). Systemic diseases with hypoxemia might also impair the ocular perfusion pressure and cause retinal hypoxia with extracellular (vasogenic edema) or intracellular (cytotoxic edema) fluid accumulation and retinal ganglion cell (RGC) death via apoptosis and excitotoxicity (15-16). COPD is one of the systemic causes of retinal hypoxia. In a recent study, a significant positive correlation was found between peripheral arterial and retinal arterial oxygen saturation as measured in blood samples and assessed with pulse oximetry (17). There are some studies showing deterioration in visual evoked potentials (VEP) and the parameters of visual field in COPD patients (9-18); however, there are no studies in the literature evaluating changes in the thickness of retinal nerve fiber layer (RNFL).

Optical coherence tomography (OCT) is a high resolution imaging device that obtains reproducible cross-sectional images of the retinal tissue and optic disc and measures RNFL thickness in various retinal diseases, glaucoma and optic neuropathies (19-22). In the present study, we compared the ONH topographic parameters and RNFL thickness of patients with severe COPD with the age- and sex-matched healthy subjects using OCT and evaluated the correlations between the arterial blood gases, respiratory function tests and the RNFL thickness parameters.

PATIENTS AND METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki was approved by the Meram Medical Faculty Ethics Committee. The patients were previously informed about the nature and possible consequences of the study. The study included 30 patients who were diagnosed as stage 3 and 4 COPD and sex- and age-matched 29 healthy control subjects. After a detailed ophthalmic examination, the ONH and RNFL thickness measurements were taken by an optical coherence tomography (OCT) (Stratus OCT-3). Arterial blood gases (pO_2 and PCO_2) were measured and respiratory functional tests [Forced expiratory volume in 1 second (FEV1) and Forced vital capacity (FVC)] via spirometry test were performed for the staging of COPD patients. The control group included healthy age- and sex-matched healthy subjects with no ocular and systemic diseases.

Participants with a history of previous intraocular surgery, eye trauma, uveitis, glaucoma, hyperopia over +4.00 D, myopia over -5.00 D, peripapillary choroidal atrophy, retinal disease such as retinal vein occlusion or other pathologies and diabetic retinopathy were excluded. The ONH and RNFL thickness measurements were taken by Stratus OCT-3 (Carl Zeiss Meditec, Inc, CA, USA). Three measurements were obtained for each eye and the best measurement with the high quality of signal strength was used for data analysis. The optic disc area, cup area, rim area, C/D area, C/D horizontal, C/D vertical, average RNFL thickness and superior, nasal, inferior and temporal RNFL thickness parameters were evaluated.

Statistical analysis

Statistical analysis was performed using the SPSS 13 software for Windows (Statistical Package for Social Science, SPSS, Inc., Chicago, IL) and the results were presented as mean ± standard deviation (SD). The parameters were compared difference between the 2 groups using independent t test and a Pearson correlation analysis was carried out to assess the correlations between respiratory functional parameters, arterial blood gases and RNFL thickness parameters. A p value <0.05 was accepted as statistically significant.

RESULTS

Baseline characteristics of the participants

COPD group included 30 patients with ages between 53-70 years (mean 59.93±5.2 years) and the control group included 29 healthy individuals with ages between 50-67 years (mean 57.38±5.3 years), with no statistically significance (p=0.07). There were 4 women (13.3%) and 26 men (86.7%) in COPD group and 9 women (31%) and 20 men (69%) in the control group (p=0.125). In COPD group, 5 patients had stage 3 and 25 had stage 4 disease. The mean visual acuities were 20/25 and 20/20 in COPD and the control groups, respectively (p= 0.21). The mean IOP was 14.23 mmHg in COPD group and 15.27 mmHg in the control group with no significant differences (p=0.47).

ONH topographic parameters and RNFL thickness values of the participants

There were no significant differences in optic disc area, cup area and rim area between subjects with and without COPD (p>0.05) (Table 1). Mean C/D vertical ratio was higher in COPD group (0.46) than the control group (0.39) (p=0.029). The average and superior quadrant RNFL thickness parameters were found to be significantly thicker in COPD subjects (114.52±7.7 µm and 141.07 ±18.2 µm, respectively) compared to the control subjects (107.9±5.4 µm and 131.31±13.6 µm, respectively) (p<0.05) (Table 1). No statistically significant difference was found in the mean RNFL thickness between patients with stage 3 and stage 4 COPD (115.07±8.13 and 111.76±4.70 µm, respectively) (p=0.39).

The results of the respiratory functions, pO_2, and pCO_2 in patients with COPD

The mean pO_2 and pCO_2 levels of COPD subjects were 58.90±9.18 mmHg and 53.05±7.91mmHg, respectively. No correlation was found between pO_2 and the mean RNFL thickness (r=-0.22, p=0.33), while a moderate correlation was found between pCO_2 and superior quadrant RNFL parameter (r= 0.53, p=0.017).

The mean FEV1 and FEV1/FVC of COPD patients was 49.77±12.74 and 55.92±17.39, respectively. No correlation was found between FEV1 and the mean RNFL thickness, whereas a high negative correlation was found between FEV1/FVC and superior quadrant RNFL parameter (r=-0.76, p=0.003).

DISCUSSION

COPD is one of the systemic causes of retinal hypoxia and was shown to have adverse effects on optic nerve and retinal functions assessed by VEP, electroretinograms (ERGs) and visual field tests. In a study by Ozge et al (9), VEP assessment showed significant abnormalities in 82.1% of COPD patients. The optic nerve involvement was thought to be associated with airway obstruction, acidosis, hypercarbia, independently from age, disease duration, smoking. In a study by Demir et al (18), visual

Table 1. The comparison of ONH and RNFL thickness parameters between COPD and healthy subjects

Parameters	COPD Group	Control Group	pvalue
Disc area(mm^2)	2.44±0.37	2.36±0.33	0.35
Cup area (mm^2)	0.57±0.35	0.43±0.23	0.084
Rim area (mm^2)	1.86±0.32	1.93±0.38	0.42
C/D area ratio	0.23±0.11	0.18±0.09	0.098
C/D vertical ratio	0.46±0.12	0.39±0.10	0.029
C/D horizontal ratio	0.5±0.14	0.44±0.13	0.11
RNFL Superior (µm)	141.07±18.18	131.31±13.63	0.024
RNFL Nasal (µm)	85.50±25.63	77±15	0.13
RNFL Inferior (µm)	143.23±16.62	141.28±10.11	0.59
RNFL Temporal (µm)	88.37±23.12	78.83±13.55	0.06
RNFL Average (µm)	114.52±7.7	107.09±5.4	<0.001

RNFL: Retina nerve fiber layer; ONH: Optic nevre head; COPD: Chronic obstructive pulmonary disease; C/D: Cup/Disc

field results were worse and VEP 100 latencies were longer in COPD subjects (p<0.05, all). In experimental models of systemic hypoxia, the outer retina was shown to be more resistant, whereas the inner layer showed the highest sensitivity towards hypoxic and / or circulatory challenges. In a study by Janaky et al (23), retina's standard ERGs [cone-(photopic) ERGs, rod-(scotopic) ERGs, oscillatory potentials (OPs) and maximal responses] and 30-Hz flicker ERGs were recorded in 14 healthy volunteers who were exposed to a 15-min simulated altitude of 5500 m. The mean levels of arterial oxygen saturation were significantly decreased (P < 0.001). There was no significant change in the amplitude or latency of the slow ERG components. However, oscillatory potentials showed a significant decrease in amplitude during hypoxic exposure with partial recovery after termination of the hypoxia. Kergoat et al (24) investigated the effects of breathing pure oxygen (O_2), carbogen, or a hypoxic gas on the pattern ERG (pERG) in 20 healthy persons. Although the amplitude and implicit time of P50 were not significantly changed with systemic hypoxia, they were depressed and delayed for N95. In a study by Tinjust et al (25), the photopic flash electroretinogram (fERG) and oscillatory potentials were recorded in 18 healthy adults under mild systemic hypoxia, 5 minutes after breathing 12% O_2 in 88% nitrogen. The latency and a-wave amplitude were not changed during the tests, while the amplitude of b-wave was decreased with hypoxia. The amplitude of OP_1, OP_2, and OP_4 potentials were stable during the tests, whereas the amplitude of OP_3 was inclined to decrease with hypoxia.

Retina is unique for visualizing the processes of axonal and neuronal degeneration. OCT allows direct measurement of RNFL thickness, macular volume for area and ONH parameters. Impairment of optic nerve perfusion and retinal microcirculation may cause RGC death and axonal loss. Hypothetically, COPD was thought to cause retinal hypoxia and related RGC death via apoptosis and excitotoxicity, which might be easily detected by OCT. There are some studies the RNFL changes have been studied. It was reported in a recent publication that the layer of ganglion cell-inner plexiform was thinner in the patients with COPD (26). However, we found increased RNFL thickness in COPD patients compared to healthy controls. Moreover, superior quadrant RNFL thickness was found to be positively correlated with pCO_2 levels, and inversely correlated with FEV1/FVC values. An explanation might be hypoxia/ischemia induced retinal and optic disc edema, which might mask possible peripapillary RNFL loss associated with RGC death. Hypoxia-ischemia was shown to upregulate mRNA and protein expression of N-methyl-D-aspartate receptor subunit 1 (NMDAR1), hypoxia inducible factor-1α (HIF-1α), glutamate receptors, vascular endothelial growth factor (VEGF), endothelial, neuronal, and inducible nitric oxide synthase (eNOS, nNOS, and iNOS) in the retina (14,27). Increased VEGF levels results in the disruption of the blood retinal barrier (BRB) in retinal capillaries and/or the retinal pigment epithelium (RPE) leading to retinal edema. One of the major component of retinal edema is considered as neuronal and/or glial swelling. Increases in NOS expression lead to an increase in the production of nitric oxide (NO), which may be toxic for the cells, and excessive release of glutamate causes excitotoxic damage to the RGCs through activation of metabotropic and ionotropic GRs. Normally, whereas RPE dehydrates the outer retina, Müller glial cells mediate the rapid water transport occurring within the inner retina. Intra- and extracellular water transport is provided by specialized membrane channels, and the most rapid water transport is regulated by transmembrane water channels termed as aquaporins (AQPs). In mammalian retina, predominant AQP is AQP4, which is expressed on the Müller glial cells (28). Müller cells maintain extracellular homeostasis inward rectifying potassium channels (Kir channels). Gliotic changes of Müller cells may be involved in the development of edema in the post-ischaemic retina (16). In animal models of retinal ischemia, ocular inflammation, retinal detachment and diabetes, Müller cells were shown to decrease the expression of their major potassium channel resulting in an impairment of the rapid water transport across their membranes and cellular edema (16,29). Other than the small number of subjects, the main limitations of this study were the lack of ocular perfusion imaging, electrophysiological tests and visual field analysis that would show the functional damage in the retina. Most of the subjects in COPD group were past or current smokers, while none of the control subjects were smokers, which might also affect the results.

In a recently published article, retinal arterial and venous diameter and thickness of the rnfl were evaluated. Only thickness of the inferior quadrant was significant in the rnfl COPD group, while no difference was observed in the other quadrants. Significant increase in thickness was detected in retinal venous calibrations (30). Ozcimen et al., were found thinner

Subfoveal choroidal thickness and RNFL thickness values in COPD group than the control group (31). In another study by Kocamış et al., they reported that there was no difference between the mean rnfl and choroid thickness values of the copd patients and the control group (32). Our study had similar results with this study.

A similar condition to COPD is obstructive sleep apnea syndrome (OSAS), a condition in which the flow of air pauses or decreases during sleeping because the airway has become narrowed, blocked or floppy. Decreased ocular perfusion related to hypoxia and vasospasm associated with OSAS was thought to cause RNFL thinning (33). OSAS was also shown to be associated with decreased RNFL thickness correlated with the severity of the disease (34,35). In another study of Adam et al (36), patients with OSAS that were of no significant difference between the control group. In the study of Tsang et al (37), visual field indices were found to be significantly subnormal, while the incidence of suspicious glaucomatous disc changes higher by four times compared to the control group. The respiratory disease index during night sleep was positively correlated with diagnosis of glaucoma (P = 0.01), intraocular pressure (P = 0.025), visual field loss variance (P = 0.03), and glaucomatous ONH changes (P = 0.001) (38).

In conclusion, The increase in pCO2 and the decrease in FEV1 / FVC indicate increased hypoxia. Peripapillary RNFL loss associated with RGC death can be masked by hypoxia / ischemia-induced retinal and optic disc edema. Increased mean RNFL thickness in COPD patients was thought to be due to retinal edema associated with increased hypoxia.

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