SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2017; 34; 68-73 DOI: 10.36141/svdld.v34i1.5392

Evaluation of choroidal thickness, retinal vascular caliber, and nerve fiber layer thickness in idiopathic interstitial pneumonia

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Abstract. *Background:* Idiopathic interstitial pneumonia (IIP) is a subtype of interstitial lung disease. Hypoxia and oxidative stress that take a role in IIP, are also thought to affect ocular structures. *Objectives:* In this study, our aim was to evaluate the retinal nerve fiber layer thickness, choroidal thickness and retinal vessel diameter using the Spectral-domain optical coherence tomography (SD-OCT) in participants with IIP. *Material and method:* A total of 35 subjects with IIP were evaluated. The ocular parameters of patients with IIP were compared with that of 35 age-sex matched healthy volunteers. All subjects underwent respiratory function testing and carbon monoxide diffusion test. Arterial blood gas analysis was performed to determine the hypoxic state. In addition to SD-OCT measurements, all participants underwent a standard ophthalmic examination including visual acuity assessment, biomicroscopy, air-puff tonometry and retinal examination. *Results:* The mean retinal arteriolar caliber (RAC) was 89.5±5.5 μm in the IIP group and 94.3±6.9 μm in the control group (p=0.002). The mean retinal venular caliber (RVC) was 131.5±11.2 μm in the IIP group and 125.2±9.2 μm in the control group (p=0.01). The mean inferior quadrant retinal nerve fiber layer (RNFL) thickness was 127.5±19.4 μm in the IIP group and 140.1±13.8 μm in the control group (p=0.003). *Conclusion:* The IIP may affect retinal vessels and nerve fiber layer. The diameter of the retinal venules was larger and the diameter of the retinal arterioles was smaller in the IIP patients when compared to the healthy controls. The inferior quadrant RNFL was significantly thinner in the IIPgroup. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 68-73)*

Key words: idiopathic interstitial pneumonia, lung disease, eye, retinal artery, retinal vein

Introduction

Interstitial lung diseases (ILD) is a heterogenous group that contains more than 200 disease processes (1). Idiopathic interstitial pneumonia (IIP) is a subtype of ILD, which includes many disease processes that have different definitions with many common and also many different characteristics (2).

IIP is further divided into Usual Interstitial Pneumonia (UIP), Nonspecific Interstitial Pneumonia (NSIP), Desquamative Interstitial Pneumonia (DIP), Respiratory Bronchiolitis-Related Interstitial Lung Disease (RB-ILD), Cryptogenic Organising Pneumonia (COP), Acute Interstitial Pneumonia (AIP), and Lymphocytic Interstitial Pneumonia (LIP) (2).

ILD is a group of diseases characterized by decreased functional capacity, dyspnea, and hypox-

Received: 25 April 2016
Accepted after revision: 7 June 2016
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emia (3). Idiopathic pulmonary fibrosis (IPF, histologically termed UIP) is the most common form of ILD and constitutes 20-30% of the ILDs (4). The pathogenesis of the disease is yet to be determined (5). IIPs other than IPF are related with regard to inflammatory events, and anti-inflammatory medication is beneficial in these cases (6). An important role of oxidative stress in the pathogenesis of IIP has also been demonstrated (7,8).

The retina has the highest oxygen-consumption tissues in the body, and it is vital to get adequate oxygen supply to the retina for normal retinal function (9,10). Spectral-domain optical coherence tomography (SD-OCT) is used for the examination of the retina. SD-OCT is a noninvasive imaging modality that has been widely employed in daily ophthalmology practice during the last decade. It provides sectional images of the retinal and optic nerve head in high resolution (11).

We believe that increased oxidative stress and hypoxia affects ocular structures in patients with IIP. In this study, our aim is to evaluate retinal nerve fiber and choroidal thickness and retinal vessel diameter using the SD-OCT technique in IIP subjects.

To the best of our knowledge, this is the first study to evaluate the diameter of retinal vessels, retinal nerve fiber, and choroidal thickness in subjects with IIP.

Material and method

Study population

Ethical approval was obtained from the Ethical Board on Human Experiments, with the approval number 60116787-020/28456. All the patients with a definitive diagnosis of IIP that were followed in the Chest Disease Department were enrolled in the study. Subjects with decompensated heart failure and diabetes mellitus were excluded from the study. Others who had undergone previous eye surgery, except for uncomplicated cataract surgery, or had uveitis or retinal or glaucoma disorders were also excluded. The individuals who participated in the study were all in a stable period. Those with exacerbations were excluded. A total of 35 subjects with IIP (16 IPF, 13 NSIP, 6 COP) were evaluated. The results were compared with the evaluations of 35 healthy volunteers of comparable age and gender distribution. All participants gave their written informed consent to the study.

Ocular examinations

One of the eyes of each subject was randomly included for the study. All subjects underwent a standard ophthalmic examination, including visual acuity assessment (Snellen chart), biomicroscopy, air-puff tonometry, retinal examination, and spectral-domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg, Germany) measurements. SD-OCT provides 40,000 A scans/second with an axial resolution of 7 μm and transversal resolution of 14 μm using a 870-nm wavelength superluminescent diode. The researchers, who used optical coherence tomography, were all blind; they did not know which group or which stage the subject was in. Subfoveal choroidal thickness (SFCT), macular thickness (MT), peripapillary retinal nerve fiber layer (RNFL) thickness, and retinal vascular caliber measurements were taken with the SD-OCT. The SFCT was measured from the inner surface of the sclera to the outer part of the hyper-reflective line corresponding to the retinal pigment epithelium (Figure 1). The chorio-scleral interface was clearly visualized in all the examinations. Only the thinnest foveal thickness was assessed for macular thickness measurements. For peripapillary RNFL analysis, the thicknesses of all the quadrants (superior, inferior, temporal, and nasal) were recorded separately; the overall mean thickness was also recorded. Retinal vascular caliber measurements were performed on the red-free optic disc analysis screen. Superior and inferior temporal retinal arterioles and venules passing through an area of one-half to one-disc diameter from the optic disc margin

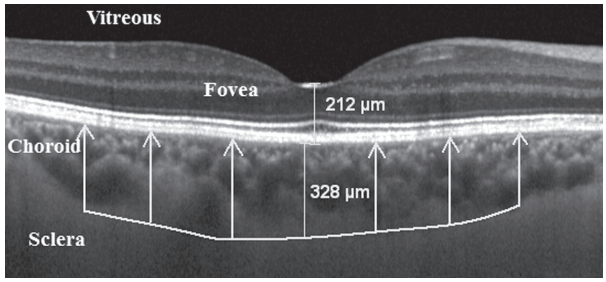

Fig. 1. Macular enhanced depth optical coherence tomography (OCT) screen of one of the patients in which the subfoveal choroidal thickness (SFCT) and foveal thickness measurements were performed. White arrows indicate the borders of the choroid

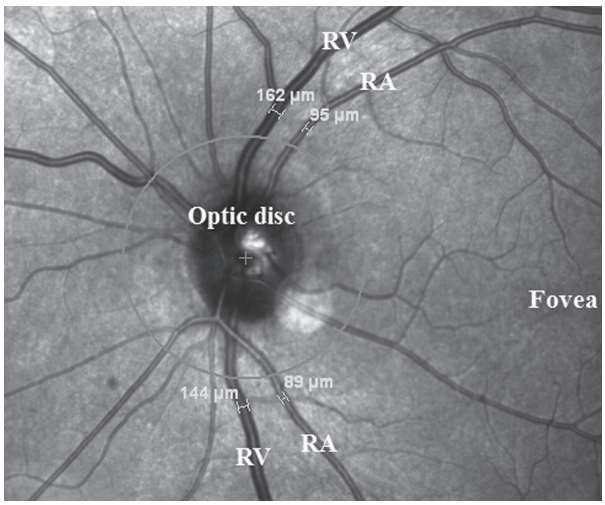

Fig. 2. The method for retinal vessel caliber measurements is shown (RA: retinal arteriole, RV: retinal venule)

were measured using manual caliper tools provided by the Spectralis software (Figure 2). The mean caliber values of retinal vessels were calculated for each eye and recorded for analysis. The intraocular pressure (IOP) was measured by an air-puff tonometer (Tonoref II, Nidek, Japan). All ocular examinations were performed in the afternoon to eliminate diurnal variations in the studied parameters.

Statistical analysis

Statistical analysis of the data using SPSS 17.0 software (SPSS Inc, Chicago, IL, USA) was performed. P values less than 0.05 were considered to be statistically significant. All data are expressed as the mean ± standard deviation of the mean. An independent sample t test was used to compare the parameters of the study and control groups. The Pearson correlation test was used to search for the significance of associations between the ocular parameters and pulmonary function tests**.**

Results

PaO2 and pulmonary function test results of patients with IIP are presented in Table 1. Some of the demographic and clinical characteristics of the participants are presented in Table 2. There were no statistically significant differences between the IIP and control groups with respect to age, gender, visual acuity, and IOP.

Table 1. PaO_2 and pulmonary function test results of patients with IIP

	Mean ± standard deviation
FEV1 (L)	1,85±0,11
FEV1% predicted	80,77±3,8
FVC (L)	2,3±0,12
FVC % predicted	78,67±3,21
FEV1/FVC ratio	85.0±5.8
PaO2 (mm/Hg)	70.3±13.6
SaO2 %	93.8±4.3
DL_{CO} %	70.9±12.2

FEV_1: Forced Expiratory Volume in the First Second, FVC: Forced Vital Capacity, PaO_2: Partial Pressure of Oxygen, SaO2: Arterial Oxygen Saturation, DL_{CO}: Carbon monoxide diffusion capacity of the lung

Table 2. Some of the demographic and clinical parameters of the participants are shown

	IIP group (n=35)	Control group (n=35)	P
Age (years)	61.3±8.9	60.1±6.7	0.53
Gender (M, F)	17 M, 18 F	17 M, 18 F	1.00
Vision (logMAR)	0.021±0.057	0.018±0.048	0.79
IOP (mmHg)	13.9±2.9	14.4±1.9	0.33

IIP: idiopathic interstitial pneumonia, M: male, F: female, IOP: intraocular pressure

The mean SFCT, MT, RAC, and RVC measurements in the IIP and control groups are shown in Table 3. The mean SFCT and MT were found to be similar in both groups, whereas the mean RAC value was markedly lower and the mean RVC value was markedly higher in the IIP group.

The mean peripapillary RNFL thickness was 100.7±9.0 µm in the IIP group and 104.9±8.0 µm in the control group (p=0.04). Table 4 shows the mean quadrant peripapillary RNFL thickness (inferior, superior, nasal, and temporal) measurements. The sta-

Table 3. The mean SFCT, MT, RAC, and RVC measurements in the IIP and control groups are shown

	IIP group	Control group	P
SFCT (µm)	269.8±84.1	284.7±69.4	0.43
MT (µm)	216.9±17.6	221.1±24.7	0.42
RAC (µm)	89.5±5.5	94.3±6.9	0.002
RVC (µm)	131.5±11.2	125.2±9.2	0.01

IIP: idiopathic interstitial pneumonia, SFCT: subfoveal choroidal thickness, MT: macular thickness, RAC: retinal arteriolar caliber, RVC: retinal venular caliber

Table 4. Quadrant peripapillary RNFL thickness (inferior, superior, nasal, and temporal) measurements are presented

	IIP group	Control group	P value
Inferior quadrant (μm)	127.5±19.4	140.1±13.8	0.003
Superior quadrant (μm)	126.6±13.9	126.5±13.7	0.98
Nasal quadrant (μm)	76.4±11.6	78.7±13.3	0.44
Temporal quadrant (μm)	72.0±12.0	74.5±9.0	0.34

IIP: idiopathic interstitial pneumonia, RNFL: retinal nerve fiber layer

tistics showed that the inferior quadrant RNFL was significantly thinner in the IIP group.

The RAC was significantly correlated with pO_2 (r=0.43, p=0.02) and sO_2 (r=0.46, p=0.02) in the IIP group. The RVC and RNFL thicknesses were not significantly correlated with the studied pulmonary parameters (p>0.05).

Discussion

Our results show that the diameter of the retinal veins was significantly larger in the IIP group than in the control group. The diameter of the retinal arterioles was found to be significantly narrower in the IIP group than in the control group. The peripapillary retinal nerve fiber layer (only inferior quadrant measurements) was found to be thinner. All of this may be due to the increase in hypoxia and oxidative stress.

Retinal vascularity is affected by various internal and external mechanical forces such as systemic blood pressure, intraocular pressure, and nerve fiber crowding in the optic disc (12). Therefore, changes in retinal blood vessels serve as markers of systemic diseases. These changes are usually arteriolar narrowing, venular expansion, arteriovenous nicking, cotton-wool spots, intraretinal hemorrhages, and papilledema (13). Stenosis of the retinal arterioles may be secondary to advanced age, systemic arterial hypertension, and coronary heart disease. Dilation of the retinal veins is secondary to diabetes mellitus, lipid disorders, smoking, and coronary heart disease (13-17). Systemic inflammation and endothelial dysfunction are thought to be responsible as the mechanisms of these changes (18,19).

Increasing fibroblast activating agents (TGF-beta, etc.) after the damaged tissue in interstitial lung disease leads to fibrosis (20). Fibrosis results consist of hypoxia and loss of vascularity. Hypoxia and vascularity loss cause endothelial dysfunction, which gives rise to pulmonary hypertension (21). Endothelial dysfunction causes pulmonary hypertension together with a decrease in nitric oxide and prostacyclin levels and an increase in endothelin and thromboxane levels (22). Pulmonary hypertension results in intrathoracic pressure increase and a decrease in venous return to the heart. The reduction of return to the heart causes deterioration of left ventricular systolic and diastolic function and the result would be the dilation of peripheral veins (21). Retinal venous dilatation can be explained by this way.

Oxygen is essential to life and plays an important role in the energy cycle of living organisms (23). Reduction of O_2 in water (H_2O) happens during normal aerobic metabolism. In the cases of incomplete reduction, unstable molecules are occurred, named by reactive oxygen species (24). Normally, there are antioxidant defense mechanisms against these composed harmful products (oxidants). Oxidant and antioxidant levels are balanced in a healthy person. Oxidative stress occurs when this balance is disrupted (23). Oxygen arrives at the retina in two ways. The first way is through the choroidal vascular bed closely connected to the back of the retina, and the second way is the retinal vascularity connecting the inner retina. The retina consumes oxygen massively and creates too many reactive oxygen molecules due to unlimited exposure to light (10).

Research shows that there is increased oxidative stress in patients with IIP (7,8). Oxidative stress also increases in eye diseases such as glaucoma (25). In glaucoma, a narrowing of retinal arteriolar and a thinning of RNFL are observed (26). In our patients, the retinal arteriolar narrowing can be explained by the increased oxidative stress. Additionally, retinal arterial narrowing can occur due to the direct effects of hypoxia, giving rise to vasoconstriction in retinal arteriolar, as in all arterial systems (27). It has already been found to correlate with the narrowing of the retinal arteries in hypoxic conditions.

SD-OCT is used widely to show RNFL thinning (28). RNFL thinning causes optic atrophy, optic neuritis, multiple sclerosis, obstructive sleep apnea, systemic arterial hypertension, Alzheimer's and Parkinson's disease (29,30). Although RFNL was found to be thinner in all the segments, it was statistically significant only in the inferior segment in our study. This result might be explained by hypoxia. Özçimen and colleagues observed RNFL thinning

in patients with COPD. The possible causes of hypoxia were connected (31). Bayhan and colleagues found RNFL thinning in patients with OSAS. The possible cause of this situation was connected to hypoxia (29). RNFL thinning in our patients can be explained by hypoxia, as in other respiratory diseases (COPD and OSAS).

While RAC and hypoxia were found to be significantly correlated in our study, RVC and RNFL were not. As the arteries are immediately affected by hypoxia directly, veins and nerves are exposed to the secondary effects of hypoxia. This situation can be explained by this way.

There were a limited number of patients participating in the study because IIP is rare and seen mostly in older age. Concomitant diseases (DM, decompensated heart failure, etc.) are also abundant. These were the biggest limitations of our study.

Hypoxia and an increase in oxidative stress can cause of the formation of eye diseases such as cataracts, retinopathy, glaucoma, and uveitis; thus, these diseases give rise to visual impairment or maybe even vision loss (23,32,33).

In conclusion, increased diameter of the retinal veins, reduced diameter of the retinal artery, and thinning of the retinal nerve fiber layer may be attributed to hypoxia in subjects with IIP. In our opinion, routine ophthalmological examinations may be suggested to IIP patients. There is no data about eye conditions of patients with IIP. Multicenter studies covering most patients with ocular manifestations of IIP should be conducted as with studies of COPD and OSAS.

Acknowledgments

The abstract of this study was presented as oral presentations in the 19th of the Turkish Thoracic Society annual congress, 6-10 April 2016, Belek-Antalya.

Author contributions:
B. K. and C. B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. U. E. contributed to the study concept and design, study supervision, data analysis and interpretation, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. A. G. and P. G. contributed to the study concept and design, data analysis and interpretation, statistical analysis, and critical revision of the manuscript for important intellectual content.

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