Evaluation of the Optic Nerve Head Using Optical Coherence Tomography Angiography in Systemic Sclerosis Patients

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Research Article

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Abstract

Introduction This study aims to quantify retinal microvascular vessel density using optical coherence tomography angiography (OCTA) in patients with systemic sclerosis (SS), whether there is a difference in values with the controls and to correlate it with the disease activity, damage risk and drug usage.

Material- method SSc patients were enrolled, and age- and gender-matched controls underwent OCTA, after basic ophthalmological and rheumatological examinations in this cross-sectional, prospective study.

Results 61 eyes of 61 consecutive SSc patients with a median age 52 years were investigeted. There was no statistically significant difference between patients and control groups regarding RNFL and OCTA measurements. As the ANA titer increases (RNFLs (p=0.01, r=-0.327), RPCwhole (p= 0.029, r= 0.279), RPCperipapiller (p=0.037, r=-0.267), RPC superior (p= 0.003, r=-0.371), RPCinferior (p=0.02, r=0.297)); there was a statistically significant decrease. RPC inside values were found to be lower in Anti Scl 70 positive patients compared to negative ones (p=0.021). RNFLn (p = 0.03), r =-0.278) value decreased as the years of disease increased. RPCinside value was found to be higher in patients using hydroxychloroquine and calcium channel blocker than those who did not use hydroxychloroquine respectively (p=0.021, p=0.027). RPC whole, RPC peripapillary, RPCnasal values were found to be statistically significantly higher in corticosteroid users than those who did not, respectivly (p = 0.043; 0.030; 0.033)

Conclusion OCTA is a safe, fast non-invasive examination and can be used to investigate subclinical eye involvement in rheumatologic diseases using single scan.

Introduction

Systemic sclerosis (SS) is a chronic multisystem disorder with vasculitis. Immune activation, vasculopathy, and excessive fibrosis are seen in the articulars and internal organs [1]. These vascular anomalies result in tissue hypoxia [2].

Endothelial cell dysfunction has been demonstrated, especially in the microvascular system [3]. Cutaneous manifestations, such as Raynaud’s phenomenon, nail fold capillary changes, and digital ulcers, have been observed as a result of vascular damage. Moreover, ischemic damage is present in other target organs, such as the heart, lung, kidney, muscles, and gastrointestinal system [4].

Optical coherence tomography angiography (OCTA) enables vascular plexus and segmentation of the inner retina, outer retina, and choriocapillaris using split-spectrum amplitude decorrelation angiography (SSADA) [5].

Previous studies found that OCTA offers large repeatability at intra- and inter-visit [6]. OCTA has also been examined in connective tissue diseases, such as systemic lupus erythematosus and vasculitis, such as

Bechet's disease [7,8].

The association of SS with glaucoma and changes in choroidal thickness has been discussed in previous studies using optical coherence tomography (OCT) [9,10]. To our knowledge, no attempt has been made to evaluate the peripapillary retinal vasculature using OCTA in SS patients.

This study quantified the retinal microvascular vessel density in SS patients using OCTA and identified whether there is a difference in values between SS patients and healthy individuals, correlating it with disease activity, damage risk, and drug usage.

Material- Method

This prospective, observational, comparative cross-sectional study was performed between July and September 2018 at Dr. Sadi Konuk Training and Research Hospital at the Health Sciences University in Bakırköy. Patients aged 20–76 who received a diagnosis of SS in the Rheumatology Department of this hospital were included in this study. The research protocols for this study were approved by the Ethics Committee of Dr. Sadi Konuk Research and Education Hospital and conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant or his/her guardian(s). The consent procedure was approved by the ethics committee. All patients fulfilled the 2013 American College of Rheumatology/ European League against Rheumatism (ACR/EULAR) criteria for SS. Whether the patients were active or in remission was determined by the Physician Global Assessment. SS was also classified as diffuse and limited, morphea, or linear based on clinical examination.

The age- and gender-matched control group consisted of healthy individuals with no history of ocular or systemic disease.

All participants underwent complete ophthalmologic examinations, including best corrected visual acuity (decimal fraction), intraocular pressure (IOP), slit-lamp examination of the anterior segment, and fundoscopic examination, conducted by the same clinician (FG). After the examination, the retinal nerve fiber layer (RNFL) and OCTA measurements were made using the RTVue device (RTVue-XR OCT; Optovue Inc., Fremont, CA, USA).

Finally, based on the files in the rheumatology clinic, the patients' age, year of diagnosis, autoantibody profile [anti-nuclear antibody (ANA) titer, anti-centromere anticore, anti-Cenp, and anti-Scl 70 positivity], systemic corticosteroid, hydroxychloroquine, calcium canal blocker, immunosuppressive agent, corticosteroid (CS), aminosalicylic acid, anti-tumor necrosis factor usage status, and ocular symptoms were recorded.

The exclusion criteria included systemic conditions that affect optic disc perfusion, such as sine-scleroderma (involvement of visceral organs in the absence of skin involvement), scleroderma overlap syndrome (SS associated with features of other connective tissue erythematosus), diabetes mellitus,

severe hypertension, and retinal diseases, as well as diseases that affect the optic disc, such as glaucoma, optic neuropathy, previous intraocular surgery or trauma, and evidence that could confound OCT interpretation, such as intraocular pressure > 21 mm Hg or oral CS use above 10 mm. Individuals with conditions that cause media opacity, such as corneal opacity, fatal dry eye syndrome, grade 3–4 nuclear cataracts, retinal microvascular abnormalities (e.g., generalized and focal arteriole narrowing, arteriovenous nicking that can interfere with hypertensive retinopathy), drusen, presence of chorioretinal scarring, and previous retinal vein occlusion, were also excluded from the study. Only images with a signal strength index > 8/10 were used for the analysis of vessel density.

OCT angiography was examined by the same person (FY) using the spectral domain OCT (RTVue-XR Avanti version 2018.0.0.14, Optovue, Fremont, CA, USA) in the morning (9:00–11:00am) to avoid possible diurnal variations. The volumetric scans were processed by the SSADA algorithm. One eye of each participant was examined and scanned during the same visit. The eye with higher image quality in OCTA measurement was included to the study.

All scans were made up of two 4.5 mm × 4.5 mm images of the optic disc area. RNFL thickness was averaged from a circular sampling profile with a diameter of 3.4 mm centered on the disc.

The peripapillary retinal area was defined as a 700-μm-wide elliptical annulus extending outward from the optic disc boundary (Fig. 1). The sectorial division of the peripapillary region was automatically performed by the OCTA device as superior and inferior hemi-radial peripapillary capillaries, and all quantitative results were recorded.

The peripapillary vessel density was defined as the proportion of the total scanned area occupied by blood vessels. These vessels were defined as pixels with decorrelation values over the threshold in the noise region, which were two standard deviations higher than the mean decorrelation value [11].

All measurements were performed using the manufacturer's tools and Analytical AngioVue software.

Statistical analysis

Data analyses were performed using SPSS software (SPSS for Windows, v. 20.0; SPSS, Inc., Chicago, IL, USA). Descriptive statistics included the mean and standard deviation for normally distributed variables and the median for non-normally distributed variables. A p value of ≤ 0.05 was considered statistically significant. The Kruskal-Wallis test was performed to compare the differences between the two groups. A chi-square test was used to analyze the frequency data on gender. Spearman correlation analysis was performed to determine the relationships between the peripapillary perfusion parameters and related factors. An independent t-test was used for comparing the normally distributed independent variables, and the Mann-Whitney U test was used for the analysis of the independent variables that did not conform to a normal distribution. Regression analysis was performed for values with significant correlations.

Results

A total of 61 eyes of 61 consecutive SS patients (59 women and 2 men), with a mean age 52 ± 12 (34–76) years, were investigated using OCTA imaging with SD-OCT.

Table 1 shows the demographics and clinical characteristics of the study.

Table 1
Demographic and clinical characteristics of subjects by groups

	SSc (n = 61)	Controls (n = 60)	p value
Age (years) (mean± SD)	51.95± 12.82	47.90±11.73	0.155*
Gender (F/M)	59/2	58/2	1.000*
BCVA (Decimal fraction) (mean± SD)	0.92±0.11	N/A	-
IOP (mmHg) (mean± SD)	15.55± 3.61	N/A	-
SSc subtype (diffuse/limited) (n)	19/42	N/A	-
Disease duration (years) (median, range)	6 (1–33)	N/A	-
Disease aktivity (remission/active)	59/2	N/A	-
ANA pattern (centromere, specled, nucleolar, homogeneous)	32/17/6/6	N/A	-
Anticenp positivity, n (%)	32 (%52.5)	N/A	-
Corticosteroid use, n (%)	15 (%73.2)	N/A	-
Immunsupresive agent use, n (%)	21 (%62.5)	N/A	-
Calcium channel blocker use, n (%)	33 (%58.9)	N/A	-
Hydroxychloroquine use, n (%)	44 (%78.6)	N/A	-
Acetylsalicylic acid, n (%)	55 (%98.2)	N/A	-
Anti-TNF drug use, n (%)	3 (%2.5)	N/A	-
Abbrevations: SSc,systemic sclerosis; SD, standard deviation; F, female; M male; IOP, intraokuler pressure; ANA (antynuclear antibody); TNF, tumour necrosis factor			
*Mann Whitney-U			

All patients were ANA positive. ANA was positive in five patients with a titer of 1/320 (8.2%), eight patients with 1/640 (13.1%), six patients with 1/1280 (9.8%), and 42 patients with 1/2560 (68.9%).

Table 2 shows the optic disc morphologic measurements (RNFL thickness and RPC values) in the SS patients and the controls.

Table 2
Optic disc morphologic parameters, RNFL thickness PRC measurements of the SS patients and control subjects

RNFL and RPC parameters	SS group	Control group	p value*
Average RNFL (µ)	111.96± 14.28 (mean±SD)	109.50 (106–114) (median 95% CI)	0.35
Superior RNFL (µ)	132.43± 18.49 (mean±SD)	130±16.91 (mean±SD)	0.83
İnferior RNFL (µ)	143.93± 18.48 (mean±SD)	140.00 (134–146) (median 95% CI)	0.425
Temporal RNFL (µ)	75.00 (69–76) (median 95% CI)	72.00 (70–79) (median 95% CI)	0.45
Nasal RNFL (µ)	100.96± 17.54 (mean±SD)	99.59± 12.46 (mean±SD)	0.17
w VD %	56.75 (56.10–58.20) (median 95% CI)	56.96± 2.07 (mean±SD)	0.34
iVD %	59.10 (58.40–62.00) (median 95% CI)	61.10 (60.30–62.60) (median 95% CI)	0.24
pVD % average %	58.95 (57.60–59.70) (median 95% CI)	58.97± 2.61 (mean±SD)	0.25
pVD superior %	52.50 (51.00–54.00) (median 95% CI)	53(52–55) (median 95% CI)	0.54
pVD inferior %	54.79± 3.57 (mean±SD)	55 (54–56) (median 95% CI)	0.43
pVD temporal %	54.50 (52.00–55.00) (median 95% CI)	54.59± 3.93 (mean±SD)	0.41

Abbrevations: SSc,systemic sclerosis; SD, standard deviation; RNFL, retinal nerve fiber layer; c/d, cup/disc ratio; RPC, radial peripapillary capillary plexus; wVD: Whole vessel density; iVD inside vessel density

*Mann Whitney-U- normal dağılmayanlar, Independent Sample T-Test- normal disturibition

mean ± SD; median (95% CI)

RNFL and RPC parameters	SS group	Control group	p value*
pVD nasal %	48.57± 4.18 (mean±SD)	50.00± 3.21 (mean±SD)	0.07
Abbrevations: SSc,systemic sclerosis; SD, standard deviation; RNFL, retinal nerve fiber layer; c/d, cup/disc ratio; RPC, radial peripapillary capillary plexus; wVD: Whole vessel density; iVD inside vessel density			
*Mann Whitney-U- normal dağılmayanlar, Independent Sample T-Test- normal disturibition			
mean ± SD; median (95% CI)			

The negative correlation between nasal RNFL and time from disease diagnosis was shown in Fig. 2.

As the ANA titer increased [RNFLavg ($p = 0.01$, $r = -0.327$), RPCwhole ($p = 0.029$, $r = 0.279$), RPCperipapiller ($p = 0.037$, $r = -0.267$), RPC superior ($p = 0.003$, $r = -0.371$), RPCinferior ($p = 0.02$, $r = 0.297$)], these values statistically significantly decreased. In addition, a non-statistically significant decrease was observed in the other RNFL and RPC values.

The RPC inside median values were found to be lower in the anti-Scl 70-positive patients compared with the negative ones ($p = 0.021$). Median: 57.25 (95% CI: 31.20–61.80).

No significant relationship was found between anti-Cenp positivity and the RPC and RNFL values ($p > 0.005$).

No correlation was found between the RNFL and RPC values, depending on whether the disease was diffuse or localized ($p > 0.005$).

Discussion

Vasculopathy in SS affects small arteries and capillaries. It reduces capillary density [12]. Sahin Atik et al. found that there was a predisposition to optic nerve head damage and glaucoma as a result of generalized vasospasm [13]. There are other studies on non-glaucomatous optic neuropathy [14]. The frequency of glaucoma in autoimmune diseases has also been linked to vascular dysregulation and has been considered to be related to endothelin-1 [15].

Allanore et al. found that the incidence of glaucomatous optic neuropathy was higher than ocular hypertension (HT), although IOP was normal in a prospective cohort study [9]. Sahin Atik et al. extended Allanore's study by examining the retinal nerve fiber and optic disc morphology using OCT in scleroderma patients who were not diagnosed with glaucoma and found that only those with a c/d ratio > 0.5 showed a statistically significant thinning in the inf RNFL quadrant [13]. Coskun et al. found a statistically

significant difference in choroidal thickness in scleroderma patients, and they attributed this to the choroidal hypoperfusion shown in the fundus floresein angiography (FFA) [16].

Serup et al. showed some changes, especially in pigment epitheliopathy and retinal arterioles, which are considered to be associated with it, and persistent hyperfluorescence in the temporal venules in the FFA [17]. Farkes et al. found some choroidal changes with endothelial damage. These changes were considered to be similar alterations to skin and renal affection and could be related to the flow in the optic nerve [18]. Although the exact cause of RPE atrophy in primary SS could not be determined, it was considered to be associated with choroidal flow and choroidal disorder secondary to hypertensive retinopathy. Usiyama et al. found that retinopathy findings were higher in normotensive SS than in the control group [19]. Grennan et al. found choroidal hypoperfusion areas in the FFA except for one patient, no HT was found [20].

Only the superficial optic nerve head vessel can be seen with the optic disc circulation in the FFA. Deep vessels cannot be seen [21]. Capillary flow in the small retina area can be measured with a laser Doppler flowmeter, but its results have been found to be variable [22]. OCTA is a reproducible technique that enables the understanding of the vascular structure of the optic disc and macula in a non-invasive manner based on flow [23]. OCTA visualizes the microvasculature by detecting motion contrast from flowing blood without dye injection [24]. OCTA has been found to be more precise in scanning macular capillaries and the RPC than FFA [25]. Many studies have been conducted using FFA, some with the Heidelberg retina flowmeter and the confocal scanning technique, to evaluate ocular blood flow. However, as some techniques are invasive, they cannot measure quantitatively and have some limitations because they cannot show the microvascular bed well [26]. The AngioVue automatically analyzes vessel density in different layers, which is its major advantage over conventional angiography.

It is known that RNFL thickness and RPC density decreases with age [27]. We selected age-matched controls to prevent them from affecting our measurements.

The quantitative data from these retinal vessels is likely be useful in analyzing metabolic activity from the retina [28]. In the current study, the decrease between the values of RNFL and RPC OCTA values and the disease duration suggests that these parameters are affected as the years of disease increase.

Although ANA is not used in SS activity, studies have pointed out ANA subsets to be useful in anticipating long-term outcomes [29]. In the current study, the increase in the ANA titer and the decrease in RNFL superior, RPC whole, peripapillary, inferior, and temporal values suggest that vascular values are affected. The decrease in the RPCinside value in anti-Scl 70-positive patients also supports this finding.

Many reasons can be attributed to the perfusion of the optic disc. The main cause is vasculopathy and immune activation, resulting in excessive fibrosis [30]. Ischemia occurs as a result of intimal fibroblastic proliferation and vasospastic episodes in SS [31]. Endothelin-1 and angiotensin 2, which are potential vasoconstrictors, are known to increase in SS patients and play a role in the vasospastic process.[32]

These structural changes and prolonged vasospasm are considered to be due to decreased blood flow [33].

Calcium channel blockers are widely used agents for reducing the frequency and severity of ischemic attacks in Reynaud's phenomenon [34]. Esen et al. found no difference in choroid thickness and central macular thickness in terms of calcium channel blocker users [10]. In the present study, the RPC inside value was found to be higher in patients using calcium channel blockers. In addition, the higher RPC values in those who use hydroxychloroquine, immunosuppressive drugs, and corticosteroids suggest that these drugs are effective against vascular density and inflamation in SS disease. Therefore, there is a need for a randomized controlled study on this subject.

To the best of our knowledge, there has been no research on OCTA that searches the optic disc RPC parameters. Only one study has investigated the RPC values in the macular region. Hekimsoy et al. conducted OCTA measurements in the macular region in patients with SS. Accordingly, the superficial capillary plexus vessel density and the deep capillary plexus vessel density of the fovea were significantly lower than those in the healthy control subjects [35].

This study is limited by the small sample size, the cross-sectional design, and the inclusion of SS patients with a relatively short follow-up period, such as a median of six years. We recommend conducting further longitudinal studies with a larger sample size and including patients diagnosed with SS for over 10 years to establish the correlation between disease activity and damage scores.

In conclusion, SS is an uncommon multisystem disorder that is related to immune activation and vasculopathy-associated complications. It results in the overproduction and accumulation of collagen and other extracellular matrix proteins. OCTA is a safe, fast, and non-invasive examination and can be used to investigate subclinical eye involvement in rheumatologic diseases using a single scan.

Declarations

Conflicts of interest:

The authors declare that there are not any competing financial or non-financial interests in relation to the work described.

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Author contribution:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sibel Zirtiloglu, Ozan Cemal Icacan, Fatih Guven and Ozge Pinar Akarsu Acar.

The first draft of the manuscript was written by Sibel Zirtiloglu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CRediT authorship contribution statement:

SIBEL ZIRTILOGLU: Conceptualization, Methodology, Formal analysis, writing - Original

draft, Writing - Review & editing, Investigation, Project administration. MUSTAFA SUAT

ALIKMA: Writing- review & editing, English translation. OZGE PINAR AKARSU ACAR: Writing- review & editing. FATIH GUVEN: Methodology. OZAN CEMAL ICACAN:

Methodology. FADIME ULVIYE YIGIT: Project administration.

Data availability:

All data and materials would be available if requested.

Ethics approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and /or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the Bakirkoy Dr Sadi Konuk Training and Research Hospital. (Approval number: 2018/316).

Animal research:

Not applicable.

Constent to participate:

Informed constent was obtained from all individual participants included in the study.

Consent to publish:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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Figures

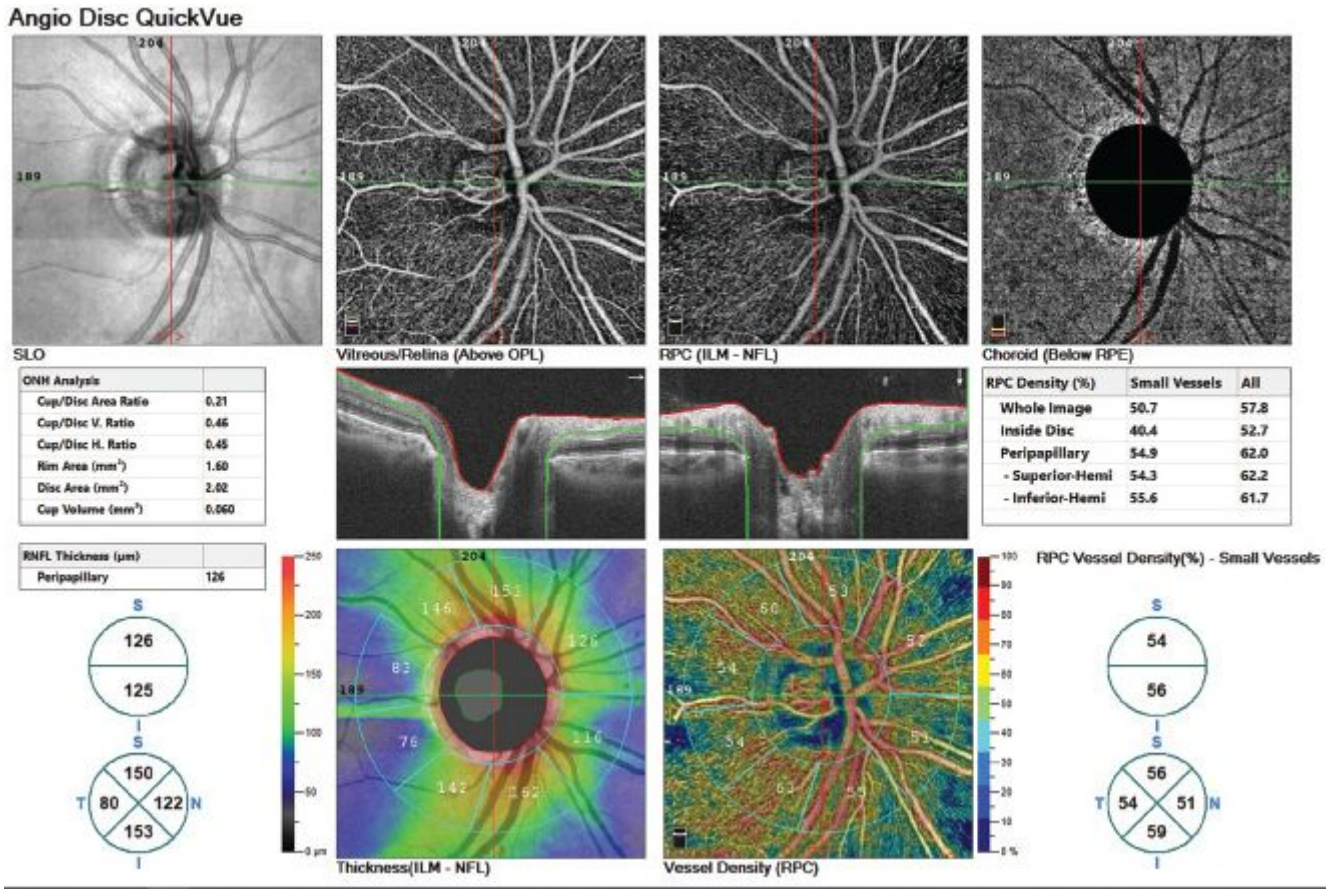

Figure 1

ONH analysis, RNFL thickness and RPC density images Footnote of Fig.1: Image downloaded from OCT device (RTVue-XR OCT; Optovue Inc., Fremont, CA, USA)

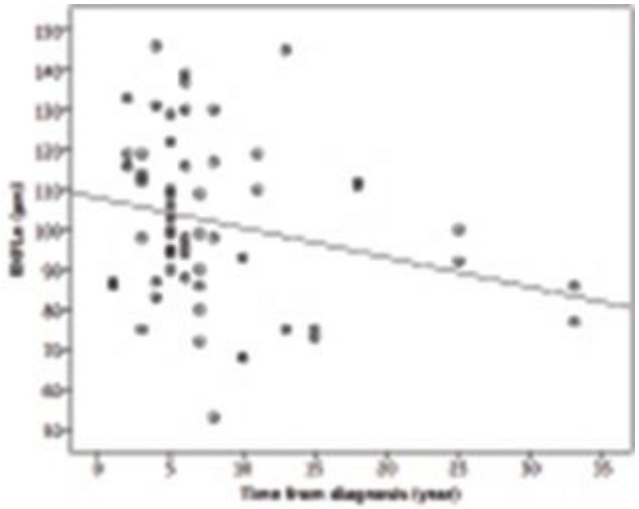

Figure 2

The correlation and regression line between nasal RNFL and time form diagnosis Footnote of Fig.2: Designed with SPSS Graphs function (SPSS for Windows, v. 20.0; SPSS, Inc., Chicago, IL, USA)

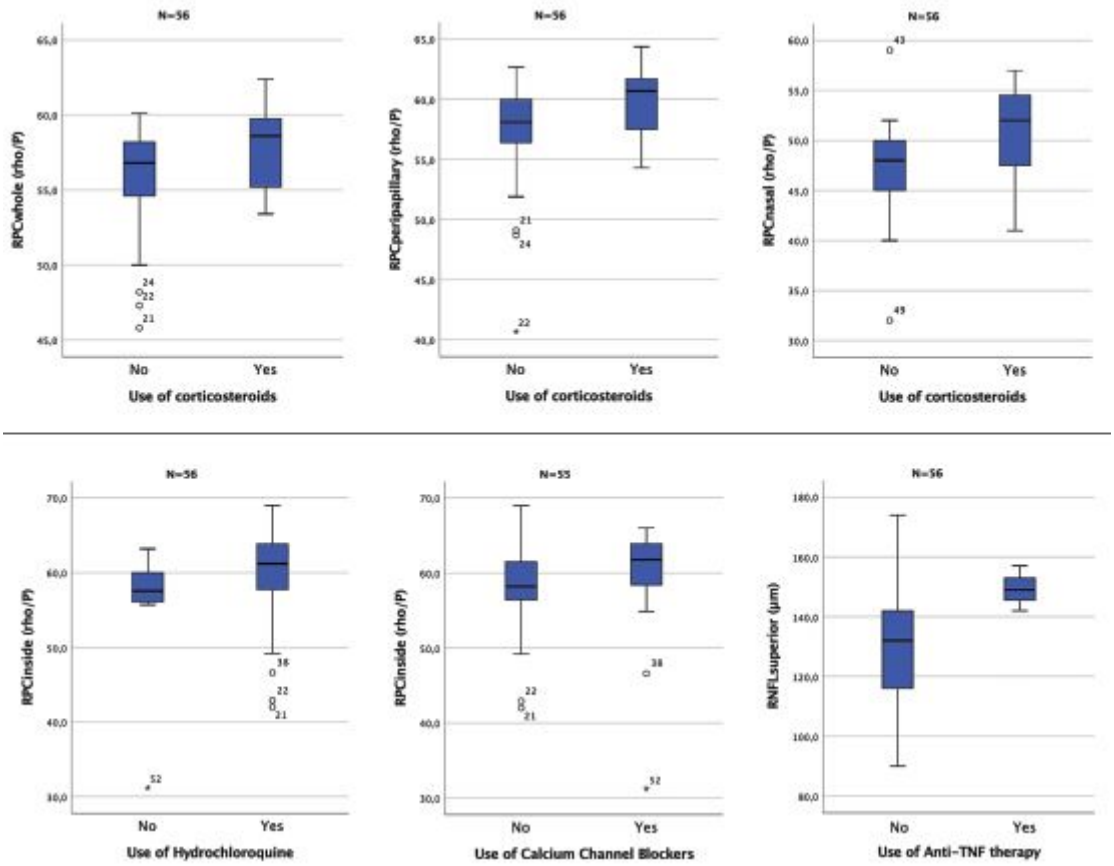

Figure 3

Optic disc changes in terms of drug use Footnote of Fig.3: Designed with SPSS Graphs function (SPSS for Windows, v. 20.0; SPSS, Inc., Chicago, IL, USA)