

Relationship between Retinal Nerve Fiber Layer Thickness and Aortic Distensibility in Peripheral Arterial Disease Patients

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ABSTRACT

Aim and objective: To evaluate the relationship between aortic distensibility (AD) and aortic stiffness B index (ASBI) with retinal nerve fiber layer (RNFL) thickness measured with HD-OCT in peripheral arterial disease (PAD) patients.

Materials and methods: Twenty-six PAD patients and 22 age-matched healthy control were enrolled. Subjects with PAD were classified into two groups. Patients with diabetes (DM) or hypertension (HT) comprised group I ($n = 18$) and without DM or HT comprised group II ($n = 8$). Color Doppler imaging was performed on all patients and PAD was diagnosed by using the ankle-brachial index (ABI). Retinal nerve fiber layer thickness values between control and PAD patients and correlations between RNFL thickness and aortic stiffness parameters (AD and ASBI) were evaluated.

Results: The inferior-nasal and inferior-temporal quadrant were the thickest in healthy subjects and the PAD group. Retinal nerve fiber layer thickness significantly decreased in superior-nasal, temporal, inferior-nasal quadrants in group I than healthy subjects ($p < 0.001$, $p = 0.005$, $p < 0.001$). Temporal and inferior-nasal quadrant thicknesses were statistically significantly thinner in group II than controls ($p = 0.02$, $p < 0.001$). The nasal RNFL quadrant was significantly thinner in group I than group II ($p = 0.014$). The correlation between RNFL thickness and aortic elasticity parameters in each group was not found to be significant.

Conclusion and clinical significance: Isolated PAD without DM or HT may lead to localized RNFL loss in temporal and inferior-nasal quadrants. Aortic elasticity parameters did not seem to be correlated with RNFL thickness in PAD.

Keywords: Aortic distensibility, Aortic stiffness, Peripheral arterial disease, Retinal nerve fiber layer.

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INTRODUCTION

Peripheral artery disease is a disease that develops due to atherosclerosis in which vessels other than cerebral and coronary arteries are involved.^{1,2} Atherosclerotic peripheral artery disease; it is a multifactorial disease that develops as a result of many risk factors that can be modified such as smoking, diabetes (DM), hypertension (HT), and cannot be modified such as sex, age, and ethnicity.³⁻⁵

Atherosclerosis is a chronic, progressive disease in which many vascular beds such as the ocular circulation and optic nerve circulation are affected.⁶

Measurement methods of noninvasive atherosclerosis are limited. These are carotid echography or radiography used to measure intimal thickness, abdominal imaging modalities, and ankle-brachial index (ABI) used to detect calcification in the aorta.⁷⁻⁹ The ABI is a simple, noninvasive, and objective test for detecting peripheral arterial disease (PAD).^{10,11}

In general, an ABI value <0.9 is accepted as an indicator of atherosclerosis.¹¹ Arterial stiffness expresses the degree of age-related vascular degeneration and decreased vessel wall elasticity, which varies as a result of different pathologies. It is an important indicator of cardiovascular risk.^{12,13} Two important parameters used in the evaluation of regional aortic stiffness are the aortic distensibility (AD) and aortic stiffness B index (ASBI).^{14,15}

Hayreh and Jonas demonstrated the association of chronic arterial HT and atherosclerosis with localized nerve fiber damage indicating optic nerve damage in experimental monkey models by detecting reduced visibility of the retinal nerve fiber layer (RNFL).¹⁶

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We herein evaluated the relationship between the AD and ASBI with RNFL thickness in PAD patients, diagnosed according to ABI.

MATERIALS AND METHODS

Twenty-six eyes of 26 patients with PAD and 22 eyes of 22 healthy controls were enrolled in our study. PAD patients were divided into two groups based on DM and HT status as follows: patients with

DM or HT (group I, $n = 18$) and patients without DM or HT (group II, $n = 8$). An age-matched control group (group III) consisted of age-matched healthy subjects. All participants were examined by the same cardiologist and ophthalmologist after they were informed and their written consent was obtained. After determining the best visual acuity with the Snellen chart of all participants, slit lamp examination, retinal, and optic nerve head examinations, and intraocular measurements (IOP) were performed. Intraocular measurements were measured three times with Goldmann applanation tonometry.

Patients with 20/20 visual acuities, normal IOPs (<21 mm Hg), and normal disc appearance were included in the study. However, patients with a known history of glaucoma, pigment dispersion or exfoliation, optic atrophy, any kind of retinopathy, neuro-ophthalmologic diseases, or media opacities preventing adequate posterior segment examination were excluded.

Ocular images of all participants were taken by the same experienced technician with HRT (Heidelberg Engineering GmbH, software version 1.4.1.0) RNFL thicknesses in a total of six quadrants [superior temporal (ST), superior nasal (SN), temporal (T), nasal (N), inferior nasal (IN), inferior temporal (IT)] were measured and analyzed in both groups.

Definition of Diabetes Mellitus and HT

Hypertensive patients were determined by systolic blood pressure (BP) over than 140 mm Hg, diastolic BP over than 90 mm Hg, or using antihypertensive medication. Patients with secondary HT were excluded from the study. Diagnosis of DM was established with fasting glucose level above 100 mg/dL or postprandial glucose above 200 mg/dL. Patients with previously diagnosed DM using systemic medications were also assumed as having DM after their medical records were controlled.

Definition of PAD and ABI Assessment

Ankle-brachial index measurements in all patients were measured with a standard Doppler USG (8 MHz KOVEN Hadeco Smartdop 20 Ultrasonic Blood Flow Detector, Japanese) from the ankle after resting for 5 minutes in the supine position.

The calculation of ABI was performed by dividing the higher of the two systolic pressures (from dorsalis pedis and posterior tibial artery) measured at the ankle to the highest systolic pressure measured from the brachial artery in the upper extremity. Ankle-brachial index ≤ 0.90 was considered pathological.¹⁷

Echocardiographic Assessment

Conventional echocardiography was used to assess the elastic features of the aorta.

All patients included in the study were examined by the same cardiologist with M mode two-dimensional echocardiography in the left lateral decubitus position. Aortic diastolic and systolic inner diameters (AoD, AoS) of the ascending aorta 3 cm above the aortic valve in the parasternal long-axis were evaluated.

Aortic stiffness index and distensibility were calculated as follows:

Aortic distensibility = $2 \times (\text{AoS} - \text{AoD}) / (\text{SP} - \text{DP}) \times \text{AoD}$ (10^{-6} $\text{cm}^2 \text{dyn}^{-1}$),

Aortic stiffness index = $\ln [\text{SP}/\text{DP}] / (\text{AoS} - \text{AoD}) / \text{AoD}$ (pure number),

ln: natural logarithm

SP: systolic pressure

DP: diastolic pressure

Statistical Analyses

Statistical analysis was performed using SPSS. Retinal nerve fiber layer thickness between each group was compared by the Mann-Whitney U test. Spearman's correlation test was performed to determine whether there was a correlation between the aortic stiffness parameter and RNFL thickness. p value <0.05 was accepted statistically significant.

RESULTS

The mean age in group I (PAD patients with DM or HT) was 62.3 ± 10.0 years (range: 42–84 years), and 63.7 ± 14.8 years in group II (PAD patients without DM or HT) (range: 32–77 years). In the healthy control group (group III), the mean age was 60.0 ± 6.7 (range: 59–62 years).

Mean ages, IOPs, and central corneal thickness (CCTs) of the patients were comparable in all groups (Table 1).

Retinal nerve fiber layer thicknesses in the healthy and PAD group are summarized in Table 2. In group I, RNFL thicknesses in the temporal, superior-nasal, and inferior-nasal quadrants were significantly thinner than in group III. Nasal RNFL thicknesses were significantly different between group I and group II. However, other quadrant thicknesses were comparable (Table 3).

Aortic distensibility and stiffness index values of all groups are shown in Table 4. Aortic distensibility was significantly decreased in the PAD patients group (groups I and II) than group III, whereas a significant increase was found for the ASBI. However, in the current study, we did not find any correlation between RNFL thickness and aortic elasticity parameters in PAD patients (Table 5).

DISCUSSION

PAH is indicative of generalized vascular atherosclerosis and often presents with atherosclerosis of lower extremity vessels. It is observed at a rate of 12–20% in the population over the age of 65 in the USA.^{18,19}

However, claudication, which is the classic main symptom of the disease, is observed in only 10% of patients.²⁰ Especially elderly patients are asymptomatic and the diagnosis of the disease can be easily missed in this group.²¹ The ABI index is a useful and reliable noninvasive method used in the diagnosis of such patients.

Its specificity is 100% and its sensitivity is 95% in the detection of stenosis in the extremity arteries.^{1,2,17}

Being highly reproducible and fast, it enables the diagnosis of the disease to be made at an early stage. Ankle-brachial index <0.9 makes the diagnosis of PAD. In this study, PAD was diagnosed in patients with an ABI <0.9 .

Systemic diseases such as DM can cause localized RNFL losses and these losses can be detected before the development of diabetic retinopathy.^{22–24}

The severity of retinopathy, the age of the patient, and the presence of systemic HT are risk factors for RNFL losses in diabetes.²⁵ Compromised in vascular reactivity and perfusion disorders cause RNFL thinning, especially in the upper quadrants.^{26,27}

Other mechanisms of early onset of DM-associated RNFL loss were reported as enhanced apoptosis of neuroglial element and retrograde axonal transport impairment.²⁸

In chronic HT, increasing vascular resistance over time can cause microvascular damage and cause atherosclerosis. Atherosclerosis

Table 1: Mean age, intraocular pressure, and central corneal thickness values in all groups

	Group I (PAD with DM/HT) n = 18	Group II (PAD without DM/HT) n = 8	Group III (Controls) n = 22	p values
Age (years)	62.3 ± 10.0 (42–84)	63.7 ± 14.8 (32–77)	60 ± 6.7 (59–62)	0.125
IOP (mm Hg)	13.7 ± 2.9 (9–18)	13.8 ± 1.0 (9–17)	13.2 ± 2.7 (10–16)	0.235
CCTs (µm)	553 ± 15.8 (510–565)	552.7 ± 11.5 (521–572)	549 ± 14.01 (533–576)	0.352

IOP, intraocular pressure; CCTs, central corneal thickness; PAD, peripheral arterial disease; DM, diabetes mellitus; HT, hypertension

Table 2: Mean RNFL thickness in all quadrants and overall for normal and PAD groups

	Group I (PAD with DM/HT) n = 18	Group II (PAD without DM/HT) n = 8	Group III (Controls) n = 22	p values (Group I–III/II–III)
TS	135 ± 22 (96–171)	120 ± 18.7 (94–151)	123 ± 18.2 (93–169)	0.06/0.96
NS	107 ± 16.6 (83–143)	115 ± 20.7 (87–145)	137 ± 26.7 (96–199)	≤0.001/0.052
T	69 ± 11 (52–104)	68.75 ± 17.6 (57–111)	77.5 ± 11 (57–98)	0.005/0.02
N	67 ± 14 (28–90)	85.12 ± 21.5 (66–127)	63.6 ± 16 (4–85)	0.623/0.081
TI	140 ± 19 (90–166)	135.1 ± 34.6 (52–158)	135 ± 21.2 (85–163)	0.712/0.062
NI	110 ± 21.9 (69–129)	112.2 ± 22.2 (77–140)	146.4 ± 14.14 (116–181)	≤0.001/≤0.001

PAD, peripheral arterial disease; DM, diabetes mellitus; HT, hypertension

Table 3: Mean RNFL thickness in PAD patients

	Group I (PAD with DM/HT) n = 18	Group II (PAD without DM/HT) n = 8	p values
TS	135 ± 22 (96–171)	120 ± 18.7 (94–151)	0.20
NS	107 ± 16.6 (83–143)	115 ± 20.7 (87–145)	0.54
T	69 ± 11 (52–104)	68.75 ± 17.6 (57–111)	0.29
N	67 ± 14 (28–90)	85.12 ± 21.5 (66–127)	0.01
TI	140 ± 19 (90–166)	135.1 ± 34.6 (52–158)	0.86
NI	110 ± 21.9 (69–129)	112.2 ± 22.2 (77–140)	0.84

PAD, peripheral arterial disease; DM, diabetes mellitus; HT, hypertension

Table 4: Aortic stiffness index and aortic distensibility values of the three groups

	Group I (PAD with DM/HT) n = 18	Group II (PAD without DM/HT) n = 8	Group III (controls) n = 22	p values
Aortic distensibility (AD)	0.18 ± 0.16 (0.04–0.64)	0.11 ± 0.05 (0.05–0.21)	0.5 ± 0.2 (0.31–1.08)	≤0.001
Aortic stiffness B index (ASBI)	52 ± 37.8 (11.69–156.17)	42 ± 35.8 (27.1–134.7)	14 ± 3.97 (8.07–22.99)	≤0.001

PAD, peripheral arterial disease; DM, diabetes mellitus; HT, hypertension

Table 5: Correlation between RNFL thickness and aortic elasticity parameters in PAD patients and the control group

	<i>TS</i>	<i>NS</i>	<i>T</i>	<i>N</i>	<i>TI</i>	<i>NI</i>
Group I (PAD with DM/HT)						
AD						
<i>p</i> value	0.310	0.874	0.920	0.355	0.556	0.648
<i>R</i> value	0.205	−0.400	−0.250	0.232	−0.149	−0.116
ASBI						
<i>p</i> value	0.286	0.701	0.463	0.788	0.984	0.748
<i>R</i> value	−0.266	−0.91	−0.85	−0.68	0.01	0.082
Group II (PAD without DM/HT)						
AD						
<i>p</i> value	0.568	0.204	0.670	0.799	0.365	0.608
<i>R</i> value	−0.204	−0.503	0.180	0.108	−0.371	0.216
ASBI						
<i>p</i> value	0.493	0.233	0.651	0.912	0.385	0.693
<i>R</i> value	0.268	0.476	−0.190	0.582	0.357	−0.167
Group III (controls)						
AD						
<i>p</i> value	0.939	0.540	0.472	0.094	0.397	0.218
<i>R</i> value	−0.017	0.148	0.162	0.366	0.199	0.274
ASBI						
<i>p</i> value	0.231	0.459	0.343	0.602	0.877	0.243
<i>R</i> value	0.266	−0.167	−0.212	−0.118	−0.35	−0.360

PAD, peripheral arterial disease; DM, diabetes mellitus; HT, hypertension

caused by HT may cause autoregulation disorders in the vascular beds, resulting in perfusion disorders in the posterior ciliary arteries and therefore the optic nerve. These conditions due to atherosclerosis result in decreased ocular blood flow and ischemic damage to the anterior optic nerve.²⁹

Hayreh found that the RNFL visibility determined by color stereoscopic fundus photographs was significantly lower in the hypertensive and atherosclerotic monkeys than in the healthy monkey group, and localized RNFL defects were significantly higher in the patient group.²⁹

In our study, we assessed the RNFL thickness in PAD patients (with DM or HT and without DM or HT) and age-matched healthy control subjects using the HRT that is a confocal scanning laser ophthalmoscope providing quantitative and real-time information about RNFL.

We found that the RNFL in PAD patients was significantly thinner than those of healthy subjects in superior-nasal, temporal, inferior-nasal quadrants ($p < 0.05$). Furthermore, nasal quadrant RNFL thickness in PAD patients with DM and HT is significantly thinner than that of PAD patients without DM or HT.

These results demonstrated that localized RNFL thicknesses are significantly decreased in PAD patients with DM or HT than controls. A decrease in RNFL thickness measurements in these patients may be explained by the ocular perfusion defects and optic disc head ischemia due to diabetes and HT.

Moreover, in PAD patients without HT and DM, RNFL measurements were found to be decreased especially in temporal and inferior-nasal quadrants compared with healthy controls. This result suggested that isolated PAD diagnosed with ABI might lead to localized RNFL loss independent of other systemic conditions like HT and DM.

Aortic distensibility ASBI is usually accepted as an indication for the early stage in atherosclerotic process.³⁰

It is shown that HT and DM have a negative impact on arterial stiffness.³⁰ We determined that PAD patients had deteriorated aortic elastic features compared with age-matched healthy subjects as expected.

Additionally, patients with PAD without HT and DM have also decreased RNFL thickness parameters. However, RNFL thickness and aortic elasticity parameters did not show any significant correlation in each group in our study.

According to literature knowledge, this study is the first to show RNFL changes in patients with isolated PAD without DM and HT diagnosed with aortic elasticity parameters (AD and ABI) and also investigating the correlation between RNFL thickness and AD and ABI in these patients. However, these results might be attributable to the small sample size of groups as a limitation of the current study. This idea might be improved and the results of the study might be supported if patients with glaucoma underwent examination by using these aortic elasticity parameters in the future.

CONCLUSION

To the best of our knowledge, this is the first study showing RNFL changes in patients with isolated PAD without DM and HT diagnosed with aortic elasticity parameters (AD and ABI) and also investigating the correlation between RNFL thickness and AD and ABI in these patients. However, these results might be attributable to the small sample size of groups as a limitation of the current study. This idea might be improved and the results of the study might be supported if patients with glaucoma underwent examination by using these aortic elasticity parameters in the future.

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