

Evaluation of the effect of high-intensity interval training on macular microcirculation via swept-source optical coherence tomography angiography in young football players

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Purpose: This study was conducted to evaluate the effect of high intensity interval training (HIIT) on macular microcirculation, measured by swept source optical coherence tomography angiography (ss OCTA) in young football players. **Methods:** Football players between 18–20 years old were included. After a detailed ophthalmological examination, physiological parameters, including height, body weight, body fat, systemic blood pressure, hematocrit values, oxygen saturation, and heart rate, were recorded. Intraocular pressure and ss OCTA parameters were measured one day before and the day after the high intensity interval training program using DRI OCT Triton (Topcon, Tokyo, Japan) between 11:00 am and 1:00 pm. **Results:** Fifteen participants completed the study. All were males with a mean age of 18.1 ± 0.4 years. Systolic and diastolic blood pressure and oxygen saturation did not change significantly ($P > 0.05$), while hematocrit levels increased remarkably ($P = 0.049$) after the HIIT program. Heart rates and intraocular pressure decreased ($P = 0.003$, $P = 0.017$, respectively). There was a significant increase in the central vessel density in deep capillary plexus (before: 18.7 ± 3.8%, after: 21.1 ± 4.5%) and central vessel density in choriocapillaris (before: 54.5 ± 2.8%, after 56.9 ± 2.2%) ($P = 0.02$, $P = 0.02$, respectively), although no changes were observed in other ss OCTA or in the central macular thickness and subfoveal choroidal thickness. **Conclusion:** A 6 week, high intensity interval training program with three exercise sessions per week seems not to alter mean superficial vascular densities, deep foveal avascular zone, and superficial foveal avascular zones, central macular thickness, or subfoveal choroidal thickness, while the central deep vascular density and central choriocapillaris vascular density increased remarkably among ss OCTA parameters.

Key words: Football players, high intensity interval training (HIIT), macular perfusion, optical coherence angiography, vascular density

Physical activity and exercise can prevent many diseases and reduce the risk of chronic diseases, mortality, and morbidity.^[1,2] To improve metabolic conditions, the American College of Sports Medicine recommends moderate-intensity aerobic exercise training for 150 min per week to prevent diseases in healthy adults.^[3] However, the proportion of individuals performing this recommended exercise is less than 20%. The biggest reason for this is insufficient time.^[4] Therefore, sports scientists, conditioners, and coaches are searching for new exercise methods that will improve the performance of athletes and health-related parameters of sedentary people in less time.^[5] Thus, high-intensity interval training (HIIT), which is thought to be more effective for improving aerobic capacity in a short period, has become prominent in recent years.

HIIT is an exercise program consisting of passive rest or low intensity, active rest periods with loads to increase the maximal heart rate to 80% and higher (three times a week, four 30-second sessions, and four minutes of rest intervals).^[6] In the HIIT program, walking, running, swimming, and cycling

activities can be applied to individuals of different form levels with different protocols.^[7] HIIT also improves physiological parameters and performance, allowing athletes to maintain their performance at over 90% VO_2 max (90% maximal oxygen uptake) for a long time.^[8,9]

Systemic blood pressure, hematocrit levels, exercise, caffeine consumption, and smoking may all affect the choroidal and retinal blood flow. Physical activity has been reported to both directly and indirectly affect the choroidal and retinal blood flow.^[10-13] Decreased choroidal and retinal blood flow is a risk factor for diseases, such as age-related macular degeneration (AMD). Therefore, a structural or functional disorder that may occur in the choroid layer may affect the retina and visual functions. Hence, changes in the microcirculation of the retina and choroid may be expected after HIIT.

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In the current literature, there are few studies about the effects of exercise on the perfusion of the choroid and retina via OCTA, and the results are inconclusive.^[13-15] We did not find studies showing the relationship between HIIT and macular perfusion with swept-source OCTA (ss-OCTA). The goal of this study was, therefore, to evaluate the effect of HIIT on macular perfusion measured by ss-OCTA in young football players and to determine the association between the changes in OCTA parameters and in physiological parameters after HIIT.

Methods

This was a prospective study conducted among young football players aged 18–20 years old who had undergone routine health check-ups at a tertiary hospital from June 2019 to August 2019. The study was approved by the Local Ethics Committee (*Prot. No: 2019/172*), and all procedures were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant, and confidentiality was maintained.

All participants underwent a detailed ophthalmological examination at the Department of Ophthalmology—including fundus examination, slit-lamp biomicroscopy, best-corrected

visual acuity, and intraocular pressure (IOP) measurement with non-contact tonometry (Topcon, Computerized Tonometer CT-1/CT-1P, Hasunma-Cho, Itabashi UK, Tokyo, Japan). The right eye of each participant was used in the study. Participants were excluded if they had a refractive error of >1 dioptres (D) of myopia, hyperopia, or astigmatism; any cardiovascular disease that would affect microcirculation; arterial hypertension; history of local or systemic medications; history of ocular trauma or surgery; glaucoma; any congenital or acquired retinal disorder (including retinal vascular disease); or the history of smoking or alcohol consumption.

Height, body weight, and body fat percentage (HF-390/00, Philips, China) were recorded. The heart rate (Polar® S810i Electro Oy, Kempele, Finland), systemic blood pressure, hematocrit values, and oxygen saturation (pO₂) (Transcend Oxy Shuttle, Sensor Medics Co., Anaheim, California, USA) were measured one day before and the day after the HIIT program between 11:00 am and 1:00 pm.

Before the baseline ss-OCTA measurements, the subjects were asked to ensure that, for at least two hours previously, no caffeine or drugs had been consumed. Any participants who did not meet these criteria were excluded from the study. All

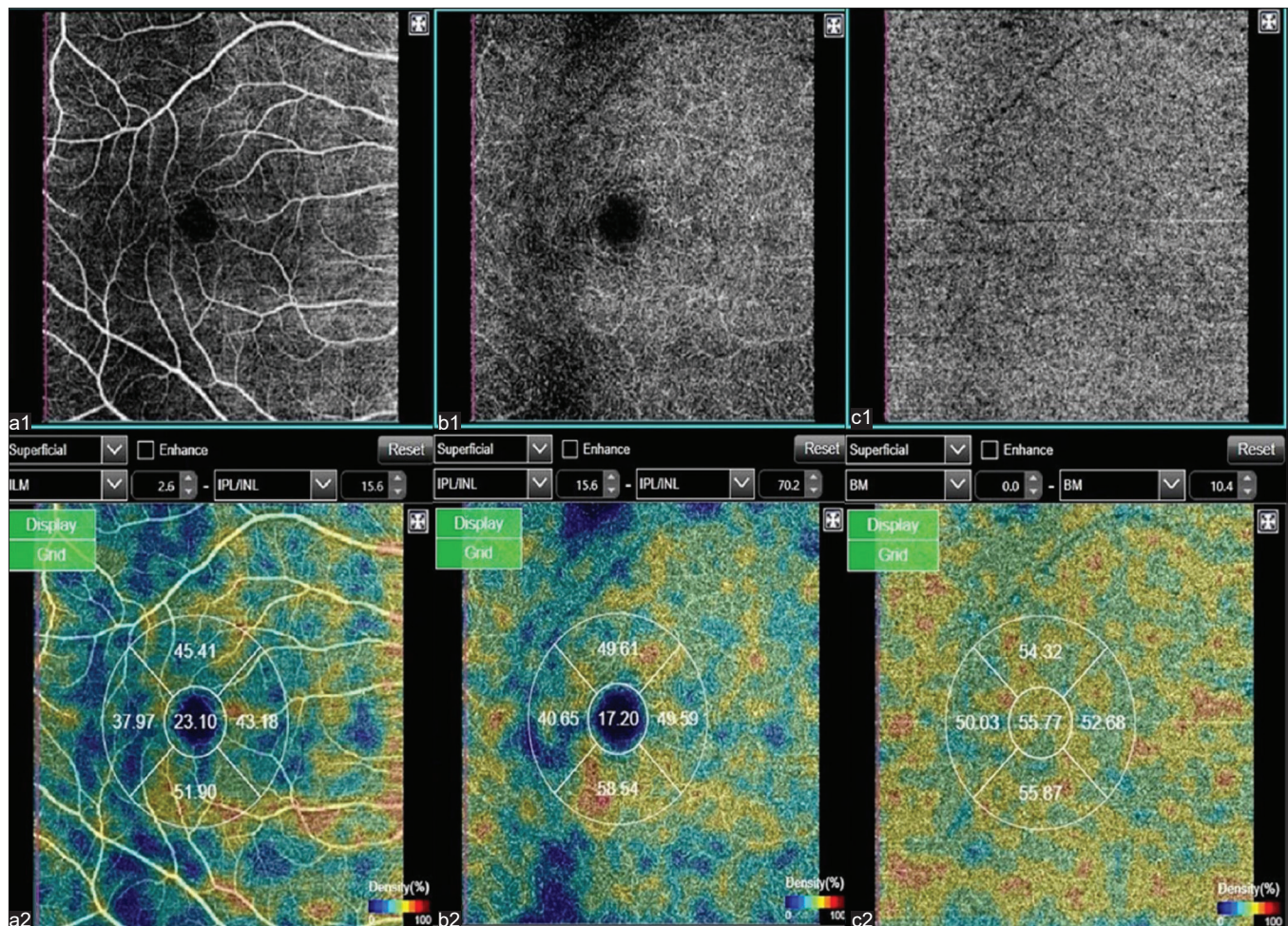


Figure 1: A 6 × 6 mm² area optical coherence tomography angiography image (a1) and density (a2) in the superficial capillary plexus and a 6 × 6 mm² area optical coherence tomography angiography image (b1) and vessel density (b2) in the deep capillary plexus. The image (c1) and the vessel density in the choriocapillaris (c2) from Bruch's membrane to 10.4 μm beneath Bruch's membrane

participants were asked to rest for ten minutes before baseline measurements.

The ss-OCTA measurements were taken one day before and the day after the six-week HIIT program with three exercise sessions per week. To avoid diurnal variations, all ss-OCTA scans were performed between 11:00 am and 1:00 pm.

High-quality images of the retinal structure and vessel network were obtained by ss-OCTA (DRI OCT Triton, Topcon, Tokyo, Japan). Scans were taken from 6 × 6 mm cubes centered on the fovea. All ss-OCTA scans and measurements were performed by one experienced operator (Y.K.). The macular scans were automatically segmented using the ss-OCTA

software (IMAGeNet 6 V.1.14.8538) into the following four 'en face' optical coherence tomography slabs:

- (1) Superficial capillary plexus from 2.6 μm beneath the internal limiting membrane to 15.6 μm beneath the interface of the inner plexiform layer and inner nuclear layer [Fig. 1. a1 and a2].
- (2) Deep capillary plexus from 15.6 μm beneath the inner plexiform layer/inner nuclear layer to 70.2 μm beneath the inner plexiform layer/inner nuclear layer [Fig. 1. b1 and b2].
- (3) Choriocapillaris from Bruch's membrane to 10.4 μm beneath Bruch's membrane [Fig. 1. c1 and c2].^[16,17]

The GNU Image Manipulation Program 2.8.14 (available in the public domain at <http://gimp.org>) was used for quantitative analysis of the foveal avascular zone area in the superficial capillary plexus (FAZs), the foveal avascular zone area in the deep capillary plexus (FAZd), the vessel density in the superficial capillary plexus (VDs), the vessel density in the deep capillary plexus (VDd), and the vessel density in the choriocapillaris (VDcc). The foveal avascular zone was defined as the area inside the central border of the capillary network, which was outlined manually for the superficial capillary plexus and deep capillary plexus using the 'Scissors' tool of the GNU Image Manipulation Program software, in accordance with the study of Kuehlewein *et al.*^[18]

Table 1: Baseline characteristics of the study participants

	Min - Max	Median	Mean±SD
Age (years)	18.0-19.0	18.0	18.1±0.4
Height (m)	1.7-1.9	1.8	1.8±0.0
Weight (kg)	61.0-83.0	72.0	71.5±6.3
BMI (high/square weight)	20.2-27.7	22.3	22.6±1.8
Body fat ratio (%)	10.2-20.0	13.0	13.5±2.3

SD: Standard deviation; BMI: Body mass index

Table 2: Comparison of parameters before and after the HIIT program.

	Pre-Exercise		Post-Exercise		P
	Mean±SD	Median	Mean±SD	Median	
Systolic (mmHg)	111.7±9.8	110.0	107.7±8.0	105.0	0.382 ^w
Diastolic (mmHg)	70.3±6.9	70.0	70.0±5.3	70.0	0.832 ^w
pO ₂ (%)	97.1±1.2	97.0	96.3±1.8	97.0	0.323 ^w
Htc (%)	44.5±2.7	45.0	45.7±3.2	46.0	0.049^p
Pulse (Bpm)	77.1±8.7	80.0	66.4±10	66.0	0.003^p
IOP (mmHg)	16.5±2.3	17.0	15.7±2.2	17.0	0.017^w
FAZs (mm ²)	248±93	244	226±136	247	0.330 ^p
FAZd (mm ²)	387±154	377	382±127	430	0.859 ^p
VDs central (%)	22.7±4.1	22.3	24.1±4.8	24.1	0.130 ^p
VDs superior (%)	50.8±3.0	51.0	51.3±3.2	51.6	0.533 ^p
VDs temporal (%)	49.3±3.1	49.2	47.5±4.1	47.8	0.169 ^p
VDs inferior (%)	50.5±4.4	50.7	51.7±3.5	52.3	0.287 ^p
VDs nasal (%)	44.2±3.9	43.8	45.4±2.7	45.7	0.158 ^p
VDd central (%)	18.7±3.8	18.5	21.1±4.5	19.7	0.002^p
VDd superior (%)	52.1±2.4	51.5	53.1±3.0	53.0	0.187 ^p
VDd temporal (%)	51.5±2.7	51.7	49.5±5.1	49.3	0.200 ^p
VDd inferior (%)	53.4±2.7	53.7	54.1±2.2	53.2	0.353 ^p
VDd nasal (%)	48.3±2.0	47.9	48.1±2.3	48.9	0.769 ^p
VDcc central (%)	54.5±2.8	54.3	56.9±2.2	57.6	0.002^p
VDcc superior (%)	54.6±1.8	54.6	54.0±2.0	54.5	0.357 ^p
VDcc temporal (%)	54.8±1.9	55.2	54.5±2.7	55.1	0.705 ^p
VDcc inferior (%)	54.8±1.5	55.1	55.4±1.2	55.4	0.096 ^p
VDcc nasal (%)	52.8±1.8	52.9	52.6±1.3	52.8	0.716 ^p
CMT (μm)	190.6±19.6	183.0	188.9±11.6	191.0	0.671 ^p
SFCT (μm)	364.3±56.3	355.0	349.2±55.4	360.0	0.097 ^p

^wWilcoxon test/^pPaired Samples *t*-test. Bold font shows statistical significance. Htc: Hematocrit; Bpm: Beats per minute; IOP: Intraocular pressure; FAZs: Superficial foveal avascular zone; FAZd: Deep Foveal avascular zone; VDs: Superficial vascular density; VDd: Deep vascular density; VDcc: Choriocapillaris vascular density; CMT: Central Macular thickness; SFCT: Subfoveal choroidal thickness

The vessel density was calculated as the percentage area occupied by flowing blood vessels in the selected region. A binary vessel image was extracted from the OCTA en face image, and vessel density was then calculated by the percentage of white pixels of vessels in the defined sectors on the binary image. Subfoveal choroidal thickness (SFCT) and central macular thickness (CMT) measurements were taken manually using enhanced high definition line scans. The measurements were performed twice, and the average of two separate measurements was used. The measurements were repeated if there was any sign of pathologic alteration in structural OCTA scans or images or if the quality of the images was poor (Image quality index < 70), and the later measurements were used.

Baseline measurements and ophthalmological examinations of the participants were conducted in the departments of ophthalmology and physiology, division of sports physiology. Afterward, the participants completed the six-week speed-based HIIT protocol^[19] training program under the supervision of their coach (F.T.). Athletes ran at 90% of the maximal heart rate (HR) for 90 sec and then walked for 90 sec, repeating the pattern for 7.5 min. Then, the athletes rested passively for 2 min. This sequence was repeated three times, for twelve 90 sec runs per session. Sessions were performed three times per week for six weeks. Heart rates were continuously monitored during training.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 22 for Windows (SPSS, Inc). The Kolmogorov–Smirnov test was used

to check the normality of the data. Physiological parameters, IOP and ss-OCTA parameters before and after HIIT were compared, either with paired t-tests for data or Wilcoxon signed rank tests according to the normality test. The right eyes of the subjects were used in the statistics. The correlations between the changes in physiological and ss-OCTA parameters were evaluated using the Spearman correlation test and, a *P* value < 0.05 was taken as statistically significant.

Results

Of the 18 young male football players, 15 participants were eligible to be included in the study. Two were excluded because of systemic drug use and a history of ocular trauma, respectively. One participant dropped out of the study since he did not come to the examination after the HIIT program. Table 1 shows the baseline characteristics of the participants. The mean parameters before and after HIIT are given in Table 2.

Comparing the results before and after the HIIT program, there was a significant difference in VDd central (before: $18.7 \pm 3.8\%$, after: $21.1 \pm 4.5\%$) and VDcc central (before: $54.5 \pm 2.8\%$, after: $56.9 \pm 2.2\%$). These increases were significant ($P = 0.002$ and $P = 0.002$, respectively) [Table 2]. No changes were observed in mean VDs, FAZs, FAZd, CMT, or SFCT after the HIIT program [Table 2].

The correlations between changes in physiological parameters and OCTA parameters are shown in Table 3. FAZd shows significant positive correlations with systolic blood pressure ($r = 0.599$, $P = 0.018$) and VDcc temporal shows significant negative correlations with systolic blood

Table 3: Correlations between the changes in physiological parameters, IOP and SS-OCTA parameters

	Systolic BP (mmHg)		Diastolic BP (mmHg)		pO ₂ (%)		Htc (%)		Pulse (Bpm)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
IOP (mmHg)	0.345	0.209	0.534	0.040	0.207	0.459	-0.050	0.859	-0.177	0.528
FAZs (mm ²)	0.069	0.808	-0.433	0.107	-0.466	0.080	-0.080	0.777	0.098	0.727
FAZd (mm ²)	0.599	0.018	0.024	0.932	-0.085	0.762	0.503	0.056	0.331	0.229
VDs central (%)	-0.097	0.730	-0.074	0.794	-0.038	0.893	0.145	0.605	0.207	0.458
VDs superior (%)	-0.161	0.567	0.086	0.761	0.167	0.552	-0.217	0.437	-0.227	0.415
VDs temporal (%)	-0.072	0.798	0.039	0.891	-0.138	0.624	-0.283	0.306	0.038	0.894
VDs inferior (%)	0.264	0.343	0.579	0.024	0.349	0.203	-0.098	0.728	-0.363	0.184
VDs nasal (%)	-0.105	0.710	0.350	0.201	0.428	0.111	0.035	0.903	-0.141	0.616
VDd central (%)	-0.213	0.446	0.085	0.764	0.310	0.260	-0.247	0.375	-0.025	0.929
VDd superior (%)	0.130	0.644	-0.315	0.253	-0.258	0.354	0.156	0.578	0.095	0.737
VDd temporal (%)	0.047	0.868	0.195	0.485	-0.514	0.050	-0.347	0.205	0.366	0.179
VDd inferior (%)	0.408	0.131	0.042	0.881	0.211	0.451	0.402	0.138	0.332	0.226
VDd nasal (%)	0.000	1.000	-0.193	0.490	-0.305	0.269	0.207	0.459	0.490	0.064
VDcc central (%)	0.105	0.710	0.077	0.784	0.094	0.738	0.124	0.661	-0.189	0.499
VDcc superior (%)	0.043	0.878	-0.446	0.096	-0.082	0.772	0.164	0.560	-0.014	0.960
VDcc temporal (%)	-0.632	0.012	-0.339	0.216	-0.343	0.211	-0.205	0.463	-0.125	0.657
VDcc inferior (%)	0.159	0.572	-0.033	0.907	0.368	0.177	0.345	0.208	0.286	0.301
VDcc nasal (%)	-0.422	0.117	-0.219	0.432	-0.261	0.347	0.040	0.888	-0.027	0.924
CMT (µm)	-0.300	0.277	-0.079	0.779	-0.078	0.782	-0.494	0.061	-0.270	0.330
SFCT (µm)	0.471	0.076	0.322	0.242	0.610	0.016	0.064	0.821	0.047	0.869

*Analysis done using Spearman's correlation test. Bold font shows statistical significance. Bpm: Beats per minute; IOP: Intraocular pressure; FAZs: Superficial foveal avascular zone; FAZd: Deep Foveal avascular zone; VDs: Superficial vascular density; VDd: Deep Vascular density; VDcc: Choriocapillaris vascular density; CMT: Central macular thickness; SFCT: Subfoveal choroidal thickness

pressure ($r = -0.632$, $P = 0.012$). Also, the changes in IOP and in VD inferior reveal significant correlations with diastolic blood pressure ($r = 0.579$, $P = 0.024$ and $r = 0.534$, $P = 0.040$, respectively). The change in SFCT was found to be correlated with the change in pO_2 ($r = 0.610$, $P = 0.016$).

Discussion

Exercise may induce physiological changes in early and long periods in the body, and these changes may differ due to exercise type. Blood is diverted to other organs and skeletal muscles during exercise, and the heart rate, and systolic and diastolic blood pressure increase, while pO_2 decreases to compensate for systemically increased energy consumption.^[13,20] However, over a long period, regular physical activity has comprehensive health benefits and is accepted as an important contribution to direct and indirect prevention of cardiovascular disease.^[21] Also, cardiorespiratory fitness (CRF) is a strong determinant of morbidity and mortality. Among athletes and the general population, it has been established that HIIT is superior to moderate-intensity continuous training for improving CRF.^[21] In the current study, we observed that hematocrit increased significantly after a 6-week HIIT with three exercise sessions per week. Although the pO_2 did not change, heart rates decreased before and after the HIIT program. Increased hematocrit levels may be caused by the body compensating for its increased oxygen demand during regular exercise. Systolic and diastolic blood pressures improved, although these changes were not statistically significant. The fact that this improvement was not statistically significant may be related to the low number of participants in the study population. A 6-week HIIT with three exercise sessions per week seems to be adequate for improving blood pressure.

Physical exercise is also protective and rehabilitative for many neuronal functions and structures.^[22] However, regarding ocular health, the direct benefits of regular physical activity are limited.^[23-29]

The indirect protective effects of physical activity may also influence diabetic retinopathy, as a clear association exists between physical inactivity, insulin resistance, and the development of type 2 diabetes mellitus.^[30] Ramos *et al.* suggested that HIIT may exert strong effects not only on insulin sensitivity but also on oxidative stress and inflammation.^[31] Thus, regular exercise reverses the subclinical impairment of the retinal microvasculature in obesity by inducing retinal arteriolar dilatation. At the molecular level, the asymmetric dimethylarginine/nitric oxide pathway may play a key role in the training-induced improvement of microvascular function, which has the potential to counteract the progression of the small vessel disease.^[32] In addition, the tropomyosin receptor kinase B signaling pathway mediates the protective effects of exercise in the diabetic rat retina.^[33]

To evaluate the exact effect of HIIT on the eye, the present study did not include subjects with any systemic disease, such as diabetes, or ocular diseases, such as AMD, which would affect systemic and ocular functions. Thus, the study included a population of wholly healthy individuals. The obese population was also excluded, and the mean BMI of participants was 22.6 ± 1.8 .

Vascular reactivity to direct stimulation of the eye, or the effects of various physiological conditions on ocular perfusion, has been studied intensively using various imaging techniques. However, to the best of authors' knowledge, this is the first study using ss-OCTA to report on changes in macular perfusion in response to a controlled physical exercise program in young football players. Macular perfusion parameters, including VDs, VDcc, FAZd, FAZs, SFCT, and CMT were evaluated before and after HIIT. To avoid individual factors and diurnal variations that might affect the results, OCTA measurements were performed between 11:00 am and 1:00 pm, and only 15 football players of similar age were included. Comparing the results before and after the HIIT program, there was an increase in the mean VDd central (before: $18.7 \pm 3.8\%$, after: $21.1 \pm 4.5\%$) and in the mean VDcc central (before: $54.5 \pm 2.8\%$, after: $56.9 \pm 2.2\%$), which were significant ($P = 0.002$, for each). No changes were observed in mean VDs, FAZd, FAZs, CMT, or SFCT after the HIIT program.

A previous study conducted by Schmitz *et al.*,^[14] using a spectral domain OCT-system (AngioVue, RTVue XR Avanti SD-OCT, Optovue, Fremont, CA, USA) to study 40 females (69.0%) who performed a 4-week HIIT program with two exercise sessions per week, reported that the mean FAZd and flow density of the superficial layer decreased by $14.00 \pm 13.02\%$ and $1.26 \pm 3.20\%$, respectively, in response to the HIIT program (pre vs. post $P < 0.0001$; $P = 0.0041$). In the same study, no statistical change in hematocrit levels was observed.^[14] Increased hematocrit is expected to cause changes in the OCTA parameters that are sensitive to erythrocytes.^[34] In the current study, only VDcc central and VDd central increased after the HIIT program. If this increase was related to the hematocrit level, a similar increase would be expected in the temporal, nasal, inferior, and superior regions. However, only central choroidal density and density in the external plexiform layer fed by the choroid increased from the baseline values after the 6-week HIIT program with three exercise sessions per week. Photoreceptors are thought to be fed from the deep capillary plexus, and this increase in VDcc central and VDd central can be interpreted as an indicator of improved blood flow at photoreceptors in the fovea.

Thus, exercise seems to especially affect the outer layers of the central retina. In the present study, a healthy population was evaluated, and the increase of VDcc central and VDd central after a 6-week HIIT program shows that retinal areas, including photoreceptors and choroid-fed retinal areas, are positively affected by this type of exercise. This was one of the few studies to study macular perfusion using ss-OCTA in response to a HIIT program, which has become a popular exercise regime in recent years. However, the research is limited because it included only young, healthy, and active football players. Hence, findings could not be generalized to a population and people with systemic and ocular pathologies or older persons. Another limitation is that the authors did not conduct research at the molecular level and did not correlate the present results with visual function tests. However, this study can be a guide for new studies that will investigate retinal and choroid responses under different exercise conditions at the molecular level.

Conclusion

A 6-week HIIT program with three exercise sessions per week seemed not to alter either mean VDs, FAZd and FAZs, CMT or SFCT, while VDD central and VDcc central increased remarkably. It is necessary to perform additional studies with varied groups of patients, including those in older age groups and those with ocular and systemic pathologies, such as systemic hypertension, diabetes, glaucoma, and AMD, to obtain more evidence on the effect of different exercises on retinal and choroidal circulation.

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Conflicts of interest

There are no conflicts of interest.

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