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The assessment of acute retinal and choroidal changes due to heavy physical exercise

Ph.D. thesis

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LIST OF ABBREVIATIONS

AMD	Age-related macular degeneration
ART	Automatic Real Time
BCDVA	Best-corrected distance visual acuity
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BP	Blood pressure
C	Central subfield of the macula
CRC	Choroid
D	Diopter
DBP	Diastolic blood pressure
ELZ+OS	Complex layer of the ellipsoid zone and the outer segment of the photoreceptors
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCC	Ganglion cell complex
GCC+ IPL	Complex layer of the ganglion cell and inner plexiform layers
HIIT	High intensity interval training
HR	Heart rate
I	Inner ring of the macula
IDZ+RPE	Complex layer containing the interdigitation zone, the retinal pigment epithelium and Bruch's membrane
IOP	Intraocular pressure
INL	Inner nuclear layer
IPL	Inner plexiform layer
NCD	Non-communicable disease
O	Outer ring of the macula
OCT	Optical coherence tomography
OCTRIMA	Optical coherence tomography retinal image analysis
ONL+IS	Complex layer containing the Henle fibers, ONL, external limiting membrane and the myoid zone of the photoreceptors
OPL	Outer plexiform layer
OR	Complex of the outer retina

RNFL	Retinal nerve fiber layer
PRL	Complex layer containing the cellular elements of the photoreceptor layer
PWR	Power-to-weight ratio
SBP	Systolic blood pressure
SD	Standard deviation
SD-OCT	Spectral-domain optical coherence tomography
SE	Spherical equivalent
T	Total macula
TR	Total retina

1. INTRODUCTION

Sedentary, inactive lifestyle considerably contributes to the increase of non-communicable diseases (NCDs), lead to the death more than 40 million individuals yearly, contributing to almost 75% of all deaths worldwide (1). NCDs are commonly referred to as chronic illnesses and typically have a prolonged duration, arising from a multifaceted interplay of genetic, physiological, environmental, and behavioral components (1). Most of the NCD-related deaths are due to cardiovascular diseases (almost 18 million annually) (1). Physical inactivity is further worsened by unhealthy diets and the harmful use of alcohol or tobacco, that in turn greatly increases the risk of NCDs, and thus makes a huge impact on modern societies. While the beneficial impacts of engaging in physical exercise on overall health are well acknowledged, it is noteworthy that the worldwide average duration dedicated to exercising remains very limited (1). For adults, the minimum of 150 to 300 minutes of moderate aerobic exercise is recommended by the WHO each week in order to promote and maintain their overall health and wellbeing (2). However, only 40 percent of the global population meets this recommendation (3).

Recently, a number of research have been dedicated to examining the impacts of sports on the human body. Either regular and acute physical activity has significant physiological impact at an organ level, in both immediate and long term. By reducing the incidence of various diseases, physical activity contributes to an increase in lifespan, exerting substantial epidemiological influence on our societies (4, 5).

A study conducted on older individuals found that engaging in regular aerobic exercise for even a period of three months resulted in a notable decrease in cardiovascular risk. This reduction was attributed to a decrease in oxidative stress and a slowdown in the progression of arterial stiffness which is commonly associated with a sedentary lifestyle and the presence of type 2 diabetes. Furthermore, it is also considered as a potential biomarker of cardiovascular risk. (6-8). Beyond the fact, that routine physical activity leads to a reduction in obesity, hypertension, serum lipoprotein, systemic inflammation and endothelial dysfunction (9), a substantial body of research, conducted on both animal models and human subjects, has demonstrated the neuroprotective effects of physical activity on the central nervous system in the context of neurodegenerative diseases

especially for conditions like Parkinson's disease, Alzheimer's diseases, amyotrophic lateral sclerosis or schizophrenia both in animal models and in humans (10-16).

Physiological response of the body to various stimuli is considerably influenced by the level of fitness. During sports activities, metabolic and circulatory changes affect the entire body, including the condition of the retina, and can consequently have an impact on vision.

1.1. The effect of physical activity on the eye and the retina itself

In research studying animal models of retinal diseases, the potential advantages of exercise have been investigated. Mild treadmill training has been shown to reduce light-induced (10000 lux) retinal degeneration in mice (17). In addition, swimming has been shown to effectively prevent ganglion cell apoptosis in a mouse model of glaucoma, highlighting its positive effects (18). Another work demonstrated, that treadmill training inhibited the cell death in the inner nuclear layer in diabetic rats induced by streptozotocin (19).

Due to its intense metabolic activity, the oxygen uptake of the retina is particularly high, which makes it vulnerable to oxidative harm. The presence of reactive oxidative species as part of the aging process has the potential to lead to the onset of many degenerative diseases. Therefore, oxidative stress may initiate age-related macular degeneration (AMD), glaucoma, or diabetic retinopathy (20, 21). Nevertheless, there is a hypothesis suggesting that participating in intense physical activity may possibly prevent the onset of AMD (22, 23). Moreover, there is evidence suggesting a favorable correlation between increased cardiorespiratory fitness and a reduced possibility of cataract formation (23). Engaging in a lifestyle defined by a nutritious diet, regular physical activity, and the cessation of smoking has the potential to provide significant advantages. Such modifications may significantly decrease the risk of developing early AMD, with a reduction factor of three (24). Moreover, performing regular physical exercise at least three times weekly has been shown to have a beneficial influence on the occurrence of neovascular AMD (25). This protective effect may be attributed to a decrease in systemic inflammation and improvement in endothelial function. This highlights the substantial impact that adopting a health-conscious lifestyle might have in preserving ocular health and perhaps delaying the emergence of severe eye disorders.

Although evidence regarding the ocular consequences of regular exercise is growing, knowledge about the immediate and short-term impacts of physical activity on the visual system is quite incomplete. A study on healthy individuals demonstrated that critical flicker frequency, which serves as an indirect measure of optic nerve function, increased after cycling and persisted for a duration of at least 30 minutes (26). Following yoga exercise, a reduction in intraocular pressure (IOP) was observed, while the macular thickness increased (27). After isometric exercise, is twice as high choroidal blood flow was detected subfoveally in patients with central serous chorioretinopathy compared to healthy controls (28). However, no information is available on the immediate chorioretinal consequences of physical activity in older adults.

1.2. Structural imaging of the retina and choroid

Optical coherence tomography (OCT) is a prevalent imaging modality employed for both the diagnosis and treatment of such ocular pathologies like glaucoma, AMD, central serous chorioretinopathy, diabetic retinopathy and macular edema, among others (29). This non-invasive, non-contact tool for assessment of the retina's structure in vivo provides high-resolution capabilities. Modern image processing methods enable the detection of almost micron-level alterations by segmenting the OCT scans according to the optical density and reflectivity of the different retinal layers. These analyses provide the assessment of individual intraretinal layer thickness in addition to the total thickness of the retina and a more precise identification of the retinal alterations, giving detailed information of many pathologies (30-32). Moreover, as a consequence of the huge number of investigations on the vascular network of the choroid, taking quantitatively analyzable images of the choroidal vessels via conventional OCT also became possible by employing enhanced depth imaging (EDI) (33-37). By increasing the depth sensitivity, this method can visualize the choroid more clearly than conventional OCT and helps to more accurately evaluate its cross-sectional structure and thickness of the choroid.

The structural evaluation of the retina has the potential to serve as an indicator of an individual's training status particularly in the field of sports medicine (38). The novel methodology arises from the concept that the complex structure of the retina has the potential to provide useful insights regarding an individual's physical training and performance capabilities. Taking part in physical activity regularly has been proposed as

having a beneficial and protective influence against various sight-threatening conditions, including AMD, glaucoma or diabetic retinopathy. By adopting a physically active lifestyle, people have the ability to reduce the occurrence and advancement of these incapacitating ocular conditions, so contributing to the overarching objective of encouraging healthy aging and lowering the prevalence of avoidable visual impairment.

Based on our theory, it is possible to introduce the concept of a "trained eye" analogous to the use of the phrase "trained heart" in the fields of cardiology and sports medicine. This concept would be associated with various retinal structural biomarkers. This use of the term “trained eye” introduces a novel perspective on evaluating training level and furthermore, it emphasizes the many advantages of physical exercise in protecting ocular health. This paradigm shift could expand the scope of sports medicine and also emphasizes the pivotal role of maintaining an active lifestyle in promoting a healthy vision and improving overall quality of life.

2. OBJECTIVES

Our purpose was to investigate the effects of acute intense physical exercise on retinal and choroidal morphology using spectral-domain optical coherence tomography (SD-OCT) imaging in sportsmen of different ages and different levels of fitness. In order to achieve this, we conducted two studies, one in young adults and one in older adults with the following objectives.

1. Assessment of the retinal and choroidal changes following intensive physical exercise in young adults**.**
2. Assessment of the retinal and choroidal changes following intensive physical exercise in senior elite athletes.

In our studies, we aimed to answer the following questions:

(i). Is there a difference between the retinal structure of the young professional sportsmen and "normally trained" young amateur sportsmen?

(ii). Which layers of the retina or the choroid change due to acute physical stress?

   i. In young adults
   ii. In senior athletes

(iii). Do retinal and choroidal thickness changes correlate with the physical load or physiological parameters (for example blood pressure or heart rate) following exercise?

   i. In young adults
   ii. In senior athletes

3. METHODS

The studies were performed at the Department of Ophthalmology, Semmelweis University in cooperation with the Department of Health Sciences and Sports Medicine, University of Physical Education, Budapest, Hungary. The study protocol was approved by the Semmelweis University Regional and Institutional Committee of Sciences and Research Ethics (272/2013). All examinations were conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all subjects.

3.1. Analysis of acute chorioretinal changes due to intensive physical exercise in young adults

3.1.1. Study participants

In a prospective uncontrolled experimental study, we recruited 21 left eyes from 21 healthy young adults aged 18 to 35 years. Fifteen of them were professional rowers from the Hungarian Rowing Federation, while six were fit individuals who engaged in vigorous physical activity (defined as an increase in heart rate [HR] to *vita maxima*) at least twice a week. Our subjects completed a survey questionnaire regarding their general and ophthalmic history, as well as the nature and frequency of their athletic participation. Anthropometric variables such as height and weight were also recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. (kg/m^2). None of the subjects were smokers.

Exclusion criteria for the participants included the history of previous ophthalmic or uncontrolled systemic diseases, ocular injury or intraocular surgery within the past 6 months, any pathologies of the macula or the optic disk on biomicroscopic examination, BCDVA worse than 20/25 examined on the ETDRS vision chart, and refractive error for far distance in ophthalmic history over ± 3D spherical equivalent (SE).

3.1.2. Ophthalmological examinations

Participants in the study underwent a comprehensive ophthalmological evaluation, which included autorefractometry, best-corrected distal visual acuity (BCDVA, measured on an ETDRS chart and expressed as Snellen equivalent), and biomicroscopic examination of the anterior and posterior segments; pupil dilation was performed with a single drop of tropicamide (5 mg/ml). Utilizing the "Enhanced Depth Imaging" protocol, volumetric OCT scans of the macula were performed using a Spectralis Spectral Domain Optical Coherence Tomography (SD-OCT, Heidelberg Engineering, Heidelberg, Germany) to optimally visualize the choroid. Sixty-one images were obtained using the posterior pole imaging option with a configuration of 30° (Horizontally), 25° (Vertically) and automatic real time (ART) of 20. A minimum scan signal strength value of 30 was required to optimize image quality.

3.1.3. Physical exercise

The subjects were asked to drink neither alcohol nor caffeine for at least 24 hours prior to exercise. The meals were not prescribed; however, all participants had consumed their usual breakfast at least one hour before the exercise. The participants arrived rested, after their usual amount of sleep, the study was performed in the morning hours.

On a rowing ergometer (Concept 2 Type D, Morrisville, VT, USA), each subject performed a progressive incremental exercise trial until exhaustion (*vita maxima*). The intensity was raised every 500 meters in the subjects rowing to compete fatigue, completing the next load phase 10 seconds quicker. In the evaluation, the utmost power achieved during the final load step was considered. The performance of each subject was expressed as the power-to-weight ratio (PWR, given in W/kg) that allows a relatively neutral comparison between subjects (39, 40). Throughout the entire exercise and the recovery period, heart rate (HR) was monitored by a Polar Rs400® monitor (Polar Electro Oy, Kempele, Finland) to prevent exceeding the maximal physiological age-related HR calculated as (220 – age) beat per minute, according to one of the most frequently applied Maffetone formula (41). Before and 5 minutes following the exercise test, blood pressure (BP) was monitored by an Omron M6 Comfort® automatic cuff sphygmomanometer (Omron Healthcare Co. Ltd., Kyoto, Japan).

3.1.4. OCT imaging and thickness data analysis

OCT imaging was performed 1, 5, 15, 30, and 60 minutes following the rowing exercise. Throughout the entire investigation, for each test, the eye tracker function was used to capture identical images of the retina. The baseline scans were set as reference, and subsequent mapping was performed at equal points.

The raw OCT data were exported from the OCT device and processed using our custom-built semiautomatic software (OCTRIMA 3D) described in detail previously (31). The software operates on a MATLAB platform (The MathWorks Inc., Natick, MA, USA), gathering thickness data of the total macular volume and 7 retinal layers from the volumetric mapping of the macula along with the thickness of the choroid based on their reflectivity. The software enables semi-automatic image processing, i.e., the automatic delineation of layer boundaries is corrected manually during the segmentation result assessment. We have previously proven the high reproducibility of the OCTRIMA 3D segmentation of macular OCT scans in healthy subjects (42). The thickness of the total retina and the following layers were recorded in the nine ETDRS regions (i.e., in the central subfield and the superior, nasal, inferior, temporal regions in the inner and the outer rings as well): the retinal nerve fiber layer (RNFL), the complex layer of the ganglion cell and inner plexiform layer (GCL+IPL), the inner nuclear layer (INL), the outer plexiform layer (OPL), the complex layer containing the Henle fibers, outer nuclear layer, external limiting membrane and the myoid zone of the photoreceptors (ONL+IS), the complex layer of the ellipsoid zone and the outer segment of the photoreceptors (ELZ+OS), the complex layer containing the interdigitation zone, the retinal pigment epithelium and Bruch's membrane (IDZ+RPE) and the choroid (CRC) consisting of the choriocapillaris, Sattler's layer and Haller's layer as far as the choroidal-scleral junction (Figure 1). The above terminology follows the recommendation of the International Nomenclature for Optical Coherence Tomography Panel (43).

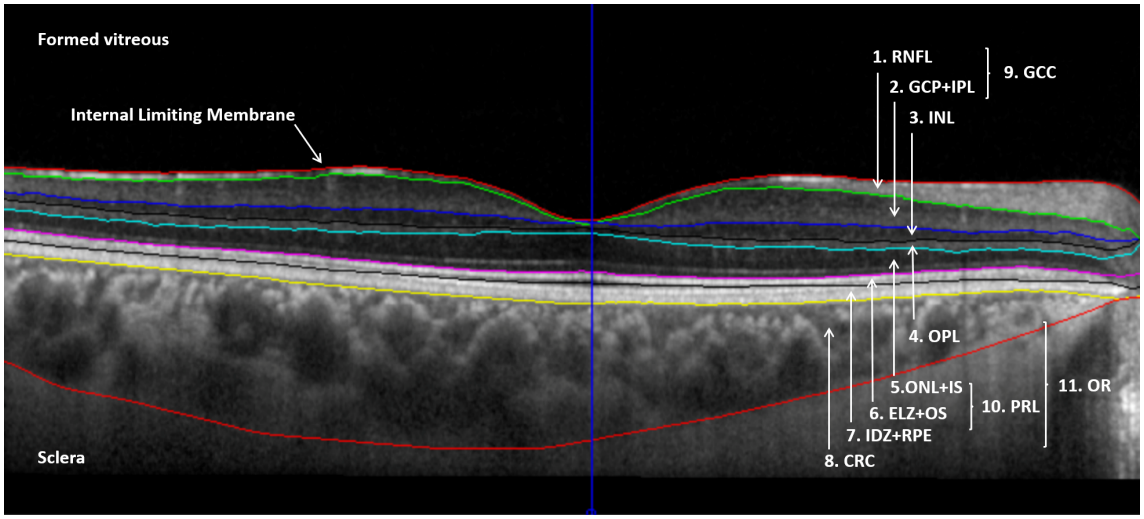

Figure 1. Segmented macular OCT image showing all boundaries segmented by the OCTRIMA 3D algorithm. The following single retinal layers and the composite layers are presented: retinal nerve fiber layer (RNFL), ganglion cell and inner plexiform layer complex (GCL+IPL), inner nuclear layer (INL), outer plexiform layer (OPL), the complex layer containing the Henle fiber layer, outer nuclear layer, external limiting membrane and the myoid zone of the photoreceptors (ONL+IS), complex layer containing the ellipsoid zone and the outer segment of the photoreceptors (ELZ+OS), complex layer containing the interdigitation zone, retinal pigment epithelium and Bruch's complex (IDZ+RPE) and choroid containing the choriocapillaris, Sattler's layer and Haller's layer as far as the choroidal-scleral juncture (CRC); ganglion cell complex (GCC), photoreceptor layer (PRL) and outer retina (OR) (44).

In addition to the single layers, composite layers, such as the ganglion cell complex (GCC, RNFL+GCL+IPL), a complex containing the cellular elements of the photoreceptor layer (PRL, ONL+IS+ELZ+OS) and a complex of the outer retina (OR, OPL+ONL+IS+ELZ+OS+IDZ+RPE), were also generated for anatomical and physiological considerations.

The same experienced graders performed all OCT segmentation tasks under the supervision of a fourth experienced grader, who made the final decision in cases of ambiguity. Following the completion of the image processing, the thickness data of the retinal layers and choroid were obtained in four distinct regions, including the total macula (T), the central subfield (1 mm in diameter, C), and the inner (I) and outer (O) macular rings (with diameters of 3 and 6 mm, I and O, respectively; Figure 2).

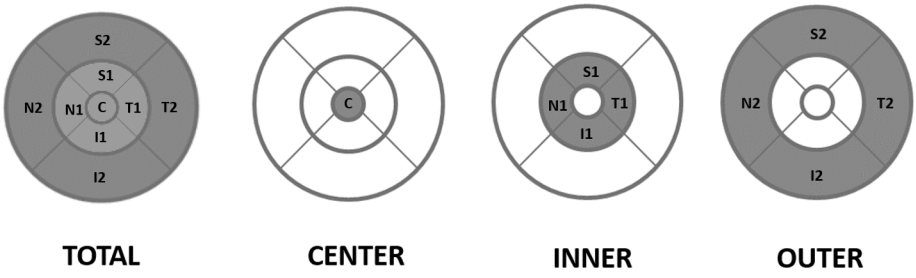

Figure 2. The four macular regions in which the layer thickness was evaluated. The total macula, the central subfield and the inner and outer macular rings (with diameters of 1, 3, and 6 mm, respectively) (45).

3.1.5. Statistical analysis

SPSS Statistics for Windows, version 17.0 software (produced by SPSS Inc., Chicago, Ill., USA) was used during all phases of the statistical analysis. In order to determine whether the data were normally distributed, the Shapiro-Wilk test was carried out. For variables with a normal distribution, Parametric tests were employed, and the mean and standard deviation (SD) were utilized to present continuously distributed data. At each time point, the differences compared to the baseline were determined for every layer thickness all variables were subjected to a one-way ANOVA test. Dunnett's post hoc test was used to compare pairwise the thickness data at various time points to the baseline measurements. The Pearson correlation coefficient was calculated to evaluate the correlation of retinal thickness changes. Multiple linear regression models using a stepwise approach were performed to identify which layers are changing together. The Pearson correlation coefficient was computed to assess the relationship between strain intensity and layer thickness changes at the 1st and 5th minute. A subgroup analysis was performed to compare the baseline characteristics of professional and amateur athletes utilizing Student’s t-test and to evaluate possible differences in layer thickness change features while controlling for age, gender, and BMI. The level of significance was set at 0.001 due to the substantial number of comparisons. However, test results with a *p*-value between 0.001 and 0.05 were also interpreted as missed significance.

3.2. The assessment of acute chorioretinal changes due to intensive physical activity in senior elite athletes

3.2.1. Study participants

Seventeen senior sportsmen (above the age of 50) were enrolled in this prospective study. Every participant affirmed to have conducted rigorous physical activity (characterized by an elevation in HR to age-matched *vita maxima*) regularly, at least twice per week, for 10 or more years. Each athlete was a member of the Hungarian Senior National Team in the discipline of track and field. All of them completed a questionnaire for their general and ophthalmic history and the type and frequency of their sports activities. Anthropometric variables such as height and weight were also documented. The BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Chronic diseases (such as hypertension or hypercholesterolemia) had to be well controlled. A legitimate sports medical certificate issued by a board-certified sports physician was required for enrollment. None of the subjects were smokers. Exclusion criteria for the participants were identical to those described in section 3.1.1 above.

3.2.2. Ophthalmological examination

All ophthalmological assessments, including chorioretinal imaging, were identical to those described in section 3.1.2 above.

3.2.3. Physical exercise

Similarly to the young athletes, all subjects were asked to drink neither alcohol nor caffeine for at least 24 hours before the exercise. The meals were not specifically designated; however, all subjects consumed their regular breakfast at least one hour before the exercise. The participants arrived rested, after their usual amount of sleep, the study was performed in the morning hours.

Contrary to the young sportsmen, each participant performed a stepwise incremental exercise trial on a cycle ergometer (Ergoline Ergoselect 200; Ergoline GmbH

Bitz) until exhaustion (age-matched *vita maxima*, see later) or reaching a peak in systolic blood pressure (SBP, exceeding 180 mmHg). Starting at 0 W, the resistance was increased every 2 minutes by 25 W, whereas the pedal turn remained constant at 60/min. The utmost power achieved (final absolute work rate) in the last load step was considered. Each subject's performance was expressed as the PWR (given in W/kg), allowing a neutral comparison between subjects (39).

Before, during, and after the entire exercise and recovery period, HR was monitored using a Polar Rs400® monitor (Polar Electro Oy) to avoid exceeding the maximum physiological age-related HR (calculated as [180 - age] per minute, according to the Maffetone formula, to provide an age-matched submaximal strain) (41). The Maffetone formula was used (over e.g., the Tanaka formula) (46) due to its somewhat lower predicted heart rate (HR) levels, which contributed to the cardiovascular safety of the senior athletes in our study. Blood pressure was measured by an Omron M6 Comfort® automatic cuff sphygmomanometer (Omron Healthcare Co. Ltd.) before, during, and 1, 5, and 30 minutes following the exercise test.

3.2.4. Layer thickness data analysis in OCT images

All OCT image processing tasks, including the segmentation, were identical to those described in section 3.1.4 above.

3.2.5. Statistical analysis

All statistical analyses were carried out in the same way as described in section 3.1.5, except for the subgroup analysis.

4. RESULTS

4.1. Assessment of the retinal and choroidal changes following intensive physical exercise in young adults

4.1.1. Demographic characteristics of the study subjects

Out of the 27 recruited young adults 25 met the inclusion criteria (1 subject had more than 3D myopia and 1 had an upper respiratory infection); however, only in 21 cases were the OCT images adequate for image assessment (15 men and 6 women; 15 professional and 6 amateurs). The mean age of the participants was 22.5 ± 4.1 years, the professionals were younger than the amateurs (20.9 ± 2.5 and 26.5 ± 4.8 years, respectively, p =0.002, missed significant). The mean height was 1.8 ± 0.1 m and amateurs were shorter than professional sportsmen (1.7 ± 0.0 vs. 1.8 ± 0.1 m, respectively, p =0.001). The professional sportsmen showed significantly higher performance compared to the amateurs (5.5 ± 0.6 vs. 3.4 ± 0.8 W/kg, respectively, p =0.000), the mean value was 5.0 ± 1.2 W/kg. Demographic data are presented in Table 1.

Table 1. Descriptive statistics of the study participants. Body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP, respectively), heart rate (HR), spherical equivalent (SE), best-corrected distance visual acuity (BCDVA), power-to-weight ratio (PWR). Data are presented as means (SD) (44). Significant correlations are highlighted in bold while missed significant results are denoted with #, n/a means no available data.

	Total (n=21)	**Professional (n=15)**	**Amateur (n=6)**	***p***
Age (years)	22.5 (4.1)	20.9 (2.5)	26.5 (4.8)	0.002 #
Gender (m/f)	15/6	12/3	3/3	n/a
Height (m)	1.8 (0.1)	1.8 (0.1)	1.7 (0.0)	**0.001**
Weight (kg)	72.7 (11.5)	74.9 (12.1)	67.2 (8.4)	0.171
BMI (kg/m2)	22.8 (2.4)	22.6 (2.6)	23.1 (2.2)	0.701
SBP (mmHg)	129.6 (14.1)	129.6 (14.5)	129.5 (14.2)	0.989
DBP (mmHg)	74.3 (7.3)	72.1 (5.8)	79.8 (8.3)	0.023 #
HR (1/min)	70.5 (13.1)	67.4 (10.5)	78.2 (16.8)	0.090
SE (D)	-0.2 (0.6)	-0.1 (0.4)	-0.6 (1.0)	0.058
BCDVA (logMAR)	-0.1 (0.1)	-0.2 (0.1)	-0.1 (0.1)	0.089
PWR (W/kg)	5.0 (1.2)	5.5 (0.6)	3.4 (0.8)	**0.000**

4.1.2. Baseline thickness data of the different retinal layers and the choroid

Professional athletes seemed to have thicker retina and choroid; however, the only significant difference was in the case of the choroid in every region (272.3 ± 43.4, p =0.001; 293.6 ± 45.0 p =0.000; 284.8 ± 43.8, p =0.001 and 267.8 ± 43.6, p =0.001, in the total macula, central subfield, inner ring and outer ring, respectively) and in the RNFL and PRL in the central subfield (13.1 ± 0.9, p =0.001; 137.3 ± 6.9, p =0.000, respectively). For the layer thickness differences between the professional and amateur sportsmen see Table 2.

Table 2. Differences between the layer thicknesses of the professional and amateur sportsmen. Data are presented as means (SD). Significant data are highlighted in bold, # denotes missed significant results (with *p*-values between 0.001 and 0.05). For the abbreviations of the layers see Figure 1 (44)

Layer	**Professional sportsmen**								**Amateur sportsmen**											
	T		**C**		**I**		**O**		**T**		***p***	**C**		***p***	**I**		***p***	**O**		***p***
RNFL	38.7	(2.9)	15.3	(1.3)	27.2	(2.0)	41.9	(3.3)	37.1	(2.6)	0.245	13.1	(0.9)	**0.001**	25.3	(1.2)	0.034 #	40.4	(3.2)	0.369
GCL+IPL	77.9	(4.0)	37.7	(6.9)	102.1	(5.0)	72.3	(4.1)	74.8	(4.0)	0.130	37.4	(9.1)	0.918	95.7	(4.9)	0.015 #	70.1	(4.3)	0.287
INL	35.2	(1.7)	19.3	(3.2)	42.1	(2.3)	33.7	(1.7)	33.0	(1.2)	0.009 #	20.5	(4.5)	0.501	39.7	(2.7)	0.049 #	31.4	(1.2)	0.008 #
OPL	24.5	(1.6)	18.6	(4.1)	26.7	(2.3)	24.1	(1.7)	25.7	(1.9)	0.162	18.9	(3.1)	0.880	26.4	(2.0)	0.811	25.8	(2.1)	0.067
ONL+IS	79.9	(5.1)	121.8	(7.5)	93.0	(6.0)	74.5	(5.1)	78.6	(4.7)	0.604	108.9	(6.4)	0.002 #	91.3	(6.1)	0.572	73.7	(4.4)	0.763
ELZ+OS	33.5	(4.5)	33.7	(2.4)	32.9	(3.8)	33.7	(4.9)	27.4	(6.6)	0.024 #	28.3	(4,2)	0.002 #	26.4	(6.2)	0.008 #	27.7	(6.9)	0.034 #
IDZ+RPE	35.0	(4.7)	42.3	(2.7)	37.0	(3.8)	34.1	(5.1)	40.9	(6.6)	0.029 #	47.9	(4.1)	0.002 #	43.5	(5.1)	0.005 #	39.9	(7.1)	0.048 #
TR	323.9	(8.7)	288.6	(14.2)	361.1	(10.7)	314.2	(8.5)	316.8	(7.1)	0.094	275.0	(13,8)	0.061	348.3	(6.6)	0.014 #	309.0	(8.2)	0.221
CRC	370.7	(54.5)	413.8	(60.8)	398.6	(60.8)	360.9	(52.9)	272.3	(43.4)	**0.001**	293.6	(45.0)	**0.000**	284.8	(43.8)	**0.001**	267.8	(43.6)	**0.001**
Composite layers																				
GCC	116.6	(6.2)	53.0	(7.9)	129.4	(6.2)	114.2	(6.5)	111.9	(6.0)	0.127	50.5	(8.6)	0.522	120.9	(5.0)	0.008 #	110.5	(7.1)	0.268
PRL	113.4	(5.4)	155.5	(8.3)	130.0	(8.3)	108.5	(8.9)	106.0	(6.9)	0.023 #	137.3	(6.9)	**0.000**	134.8	(8.5)	0.251	113.6	(9.1)	0.252
OR	172.9	(5.2)	216.3	(8.0)	189.06	(7.3)	207.1	(12.5)	172.7	(7.8)	0.940	204.1	(7.8)	0.005 #	187.7	(8.3)	0.602	213.1	(14.1)	0.347

4.1.3 Correlations between demographic characteristics and baseline layer thickness values.

The baseline thickness data was not influenced by BCDVA and gender over the whole cohort. There was a positive association seen between weight and the baseline INL in the outer ring, as well as the entire macula. Positive correlation was found between height and the baseline ONL+IS in the central region. There was a negative correlation between diastolic blood pressure (DBP) and the baseline ELZ+OS in both the inner ring and the entire macula. The aforementioned correlations, as well as correlations that did not reach statistical significance, are also interpreted in Tables 3a and 3b. There seemed to be an inverse relationship between age and the thickness of the outer retinal layers and the choroid. In contrast, the findings indicated a positive correlation between height and choroidal thickness along with DBP and thickness of the outer retinal layers.

Table 3a. Correlations between demographic characteristics and baseline layer thickness values in single layers. The table shows the Pearson correlation coefficients with the corresponding *p*-values. Significant data are highlighted in bold; # denotes missed significant results (with *p*-values between 0.001 and 0.05). Only layers with any significant or missed significant correlations are shown. For the abbreviations of the layers see Figure 1 and Table 1 (44).

	Age		**SE**		**Height**		**Weight**		**PWR**		**HR**		**DBP**	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
RNFL_T	-0,299	0.187	0.052	0.821	0.026	0.912	-0.147	0.526	-0.103	0.656	-0.450	0.040 #	-0.015	0.950
RNFL_C	-0.507	0.019 #	0.302	0.184	0.247	0.281	-0.014	0.953	-0.357	0.112	-0.424	0.055	-0.309	0.173
RNFL_I	-0.310	0.172	0.127	0.582	0.159	0.491	-0.156	0.500	-0.037	0.874	-0.484	0.026 #	-0.116	0.616
GCL+IPL_I	-0.338	0.134	0.387	0.083	0.467	0.033 #	0.335	0.137	0.367	0.102	-0.186	0.420	-0.017	0.943
INL_T	-0.222	0.334	0.275	0.228	0.542	0.011 #	0.665	**0.001**	0.342	0.129	-0.103	0.658	-0.095	0.684
INL_C	0.286	0.209	0.139	0.548	-0.123	0.595	-0.007	0.977	-0.265	0.245	0.174	0.450	0.450	0.041 #
INL_I	-0.174	0.451	0.397	0.075	0.464	0.034 #	0.525	0.015 #	0.380	0.089	-0.051	0.826	0.104	0.655
INL_O	-0.241	0.294	0.187	0.418	0.530	0.014 #	0.658	**0.001**	0.173	0.453	-0.126	0.585	-0.200	0.385
ONL+IS_C	-0.374	0.095	0.085	0.715	0.654	**0.001**	0.305	0.179	-0.214	0.352	-0.326	0.149	-0.390	0.081
OPL_C	-0.125	0.589	0.148	0.522	-0.286	0.210	-0.125	0.590	-0.552	0.009 #	0.047	0.841	0.109	0.638
ELZ+OS_T	-0.565	0.008 #	0.202	0.379	0.124	0.592	0.212	0.356	0.215	0.349	-0.244	0.287	-0.652	**0.001**
ELZ+OS_C	-0.632	0.002 #	0.184	0.425	0.271	0.235	0.088	0.704	-0.113	0.627	-0.453	0.039 #	-0.545	0.011 #
ELZ+OS_ I	-0.626	0.002 #	0.233	0.308	0.186	0.420	0.213	0.355	0.062	0.791	-0.271	0.234	-0.664	**0.001**
ELZ+OS_O	-0.541	0.011 #	0.192	0.404	0.103	0.656	0.213	0.355	0.091	0.695	-0.229	0.318	-0.644	0.002 #
IDZ+RPE_T	0.476	0.029 #	-0.174	0.451	-0.119	0.606	-0.251	0.273	-0.134	0.563	0.393	0.078	0.543	0.011 #
IDZ+RPE_C	0.512	0.018 #	-0.244	0.287	-0.410	0.065	-0.236	0.304	-0.314	0.165	0.535	0.012 #	0.352	0.117
IDZ+RPE_I	0.548	0.010 #	-0.199	0.388	-0.247	0.281	-0.284	0.213	-0.113	0.627	0.475	0.030 #	0.567	0.007 #
IDZ+RPE_O	0.450	0.041 #	-0.163	0.480	-0.080	0.732	-0.239	0.298	0.106	0.647	0.362	0.106	0.532	0.013 #

Table 3b. Correlations between demographic characteristics and baseline layer thickness values in composite layers. The table shows the Pearson correlation coefficients with the corresponding *p*-values. The sign # denotes missed significant results (with *p*-values between 0.001 and 0.05). Only layers with any significant or missed significant correlations are shown. For the abbreviations of the layers see Figure 1 and Table 1 (44).

	Age		**SE**		**Height**		**Weight**		**PWR**		**HR**		**DBP**	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
PRL_T	-0.616	0.003 #	0.036	0.877	0.261	0.253	0.170	0.461	0.248	0.273	-0.324	0.152	-0.622	0.003 #
PRL_C	-0.513	0.018 #	0.130	0.575	0.616	0.003 #	0.275	0.228	-0.217	0.344	-0.414	0.062	-0.496	0.022 #
OR_C	-0.445	0.043 #	0.110	0.635	0.451	0.040 #	0.179	0.436	-0.218	0.342	-0.251	0.273	-0.401	0.072
CRC_T	-0.542	0.011 #	0.504	0.020 #	0.514	0.017 #	0.128	0.582	0.272	0.233	-0.031	0.895	-0.341	0.130
CRC_C	-0.474	0.030 #	0.426	0.054	0.577	0.006 #	0.156	0.500	0.283	0.214	-0.146	0.526	-0.295	0.195
CRC_I	-0.519	0.016 #	0.447	0.042 #	0.531	0.013 #	0.114	0.622	0.419	0.058	-0.116	0.617	-0.332	0.142
CRC_O	-0.550	0.010 #	0.524	0.015 #	0.503	0.020 #	0.130	0.574	0.217	0.345	0.004	0.986	-0.344	0.126

4.1.4. Postexercise thickness changes of the chorioretinal layers

We observed a significant thinning of the total retina 1 minute post-exercise (-7.3 ± 0.6 µm, p <0.001), which was followed by a significant thickening at 5 and 15 minutes (+3.6 ± 0.6 µm and +4.0 ± 0.6 µm, respectively, for both p <0.001). By 30 minutes, total retinal thickness returned to baseline. These changes were also significant in the inner and outer ring, but not in the central subfield (Figure 3).

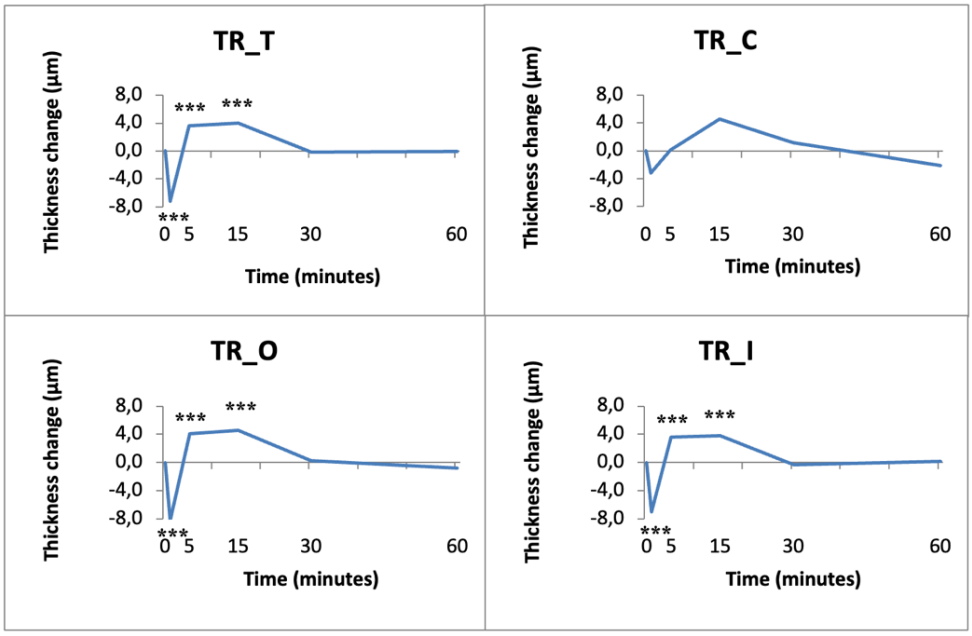

Figure 3. Changes of total retinal thickness (TR) over time following vita maxima strain of the study participants. Data are shown in the total macular area (T), the central subfield (C), the inner (I), and outer ring (O). ***: p <0.001 (44).

This trend above was present throughout the most layers of the retina, with significant changes in the GCL+IPL layer complex at 1, 5 and 15 minutes (-1.3 ± 0.1 µm, +0.6 ± 0.1 µm and +0.7 ± 0.1 µm, respectively, p <0.001 for all), in the INL at 1 and 5 minutes (-0.8 ± 0.1 µm and +0.8 ± 0.1 µm, respectively, p <0.001 for both), in the ONL+IS at 1, 5, 15 and 60 minutes (-1.4 ± 0.4 µm, p =0.003; +2.3 ± 0.4 µm, p <0.001; +1.1 ± 0.1 µm, p =0.031; and -1.1 ± 0.4 µm p =0.044, respectively) and in the IDZ+RPE

complex at 1 and 15 minutes (-3.3 ± 0.4 µm and +1.8 ± 0.4 µm, respectively, p <0.001 for both) (Figure 4).

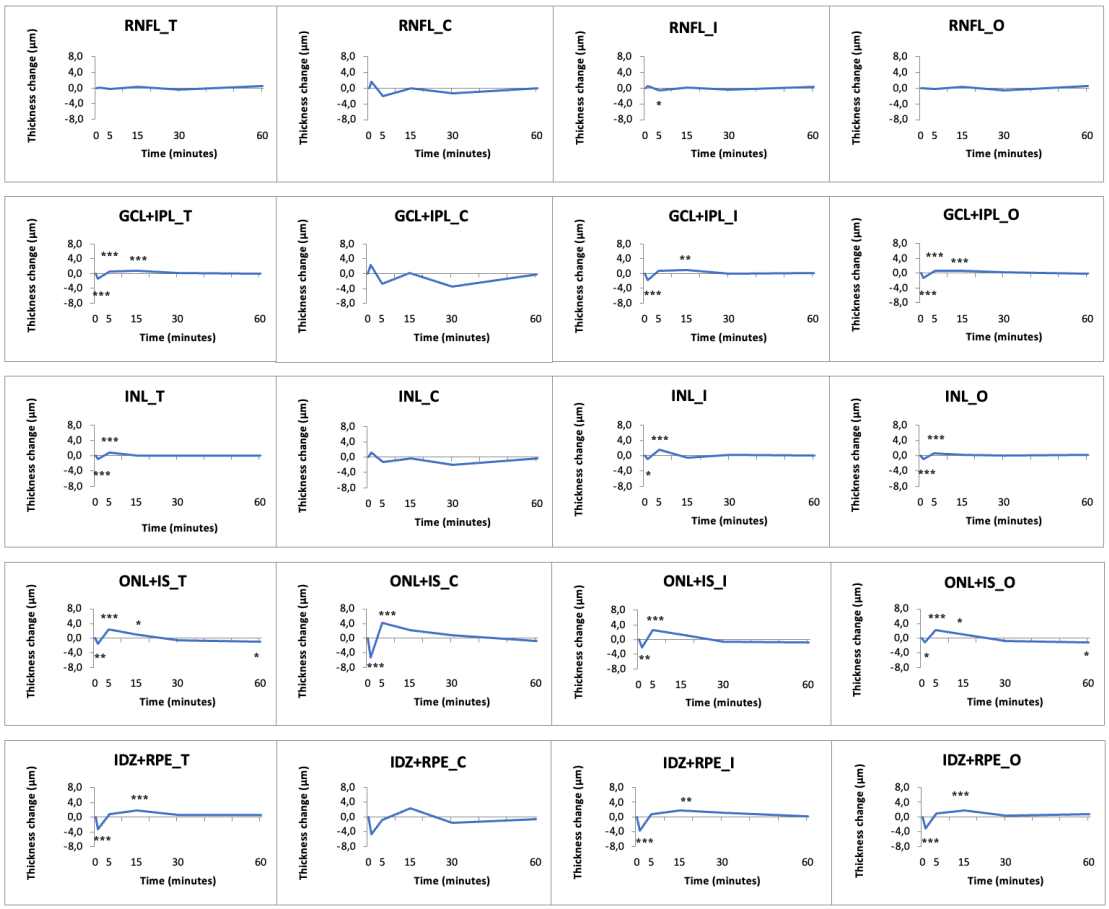

Figure 4. Changes of single retinal layer thickness over time following vita maxima strain of the study participants. Data are shown in the total macular area (T), the central subfield (C), the inner (I) and the outer ring (O). *: p <0.05 (missed significance), **: p <0.01 (missed significance), ***: p <0.001 (significant). For the abbreviations of the layers, see Figure 1 (44).

We assessed the physiologically different parts of the retina as composite layers, as well (GCC, PRL, and OR). The GCC thickness changes were significant for the total macula and outer rings at 1 minute, while missed significance was detected at 1 minute in the inner ring, and at 15 minutes in the total macula, the inner and outer ring. In the case of the PRL and OR, there were significant changes in the total macular thickness and all three macular regions at 1, 5, and 15 minutes, as well (Figure 5).

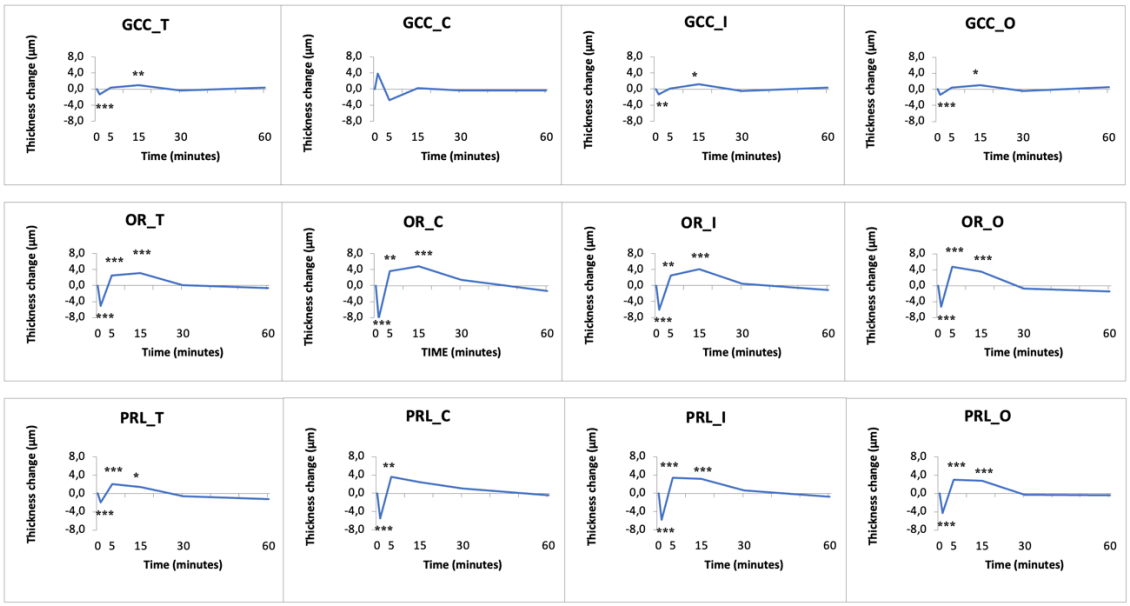

Figure 5. Changes observed in the composite layers of the macula. Data are shown in the total macular area (T), the central subfield (C), the inner (I), and outer ring (O). From top to bottom: GCC (RNFL+GCL+IPL), OR (OPL+ONL+IS+ELZ+OS+IDZ+RPE), and PRL (ONL+IS+ELZ+OS). *: p <0.05 (missed significance), **: p <0.01 (missed significance), ***: p <0.001 (significant). For the abbreviations of the layers, see Figure 1 (44).

No significant change was observed in choroidal thickness; however, we could detect a tendency towards thinning at 1, 15, and 30 minutes following exercise, with thickening at 5 and 60 minutes. (Figure 6) The absolute changes in choroidal thickness did not show any correlation with the thickness changes of the intraretinal layers.

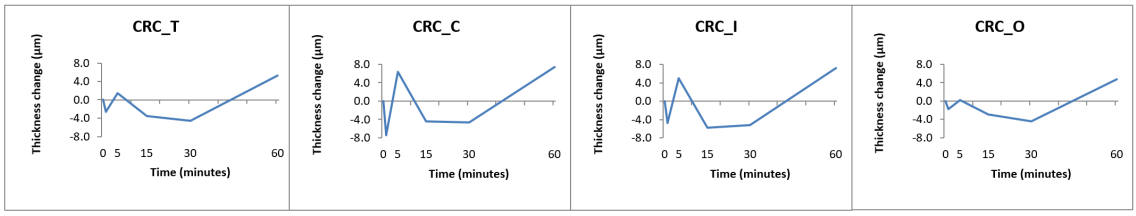

Figure 6. Changes observed in the choroid (CRC) over time following vita maxima strain of the study participants. The changes were not statistically significant; from left to right, macular area (T), central subfield (C), inner (I), and outer rings(O). For the abbreviations of the layers, see Figure 1 (44).

4.1.5. Confounding factors

The analysis of multiple linear regression showed no significant confounding variables. After controlling for confounding factors such as gender, height, weight, BMI, SBP, and fitness level, the comparison between amateur and professional athletes did not reveal any statistically significant differences. Nevertheless, it is worth noting that a significant association between PWR and any layer thickness changes was only seen in the INL in the central subfield after 5 minutes. Table 4 presents the correlation coefficients and the "missed significant" *p*-values. A significant difference was observed in PWR between athletes and amateurs (5.5 ± 0.6 vs. 3.4 ± 0.8 Watt/kg, respectively, $p < 0.001$).

Table 4. Correlation between the power-to-weight ratio and the layer thickness changes at 1 and 5 minutes of the recovery period for the total retina and three macular areas (T, total macula, C, central subfield, I, inner ring, O, outer ring). Only significant and missed significant Pearson correlations observed at 1 and 5 minutes post-exercise are shown (highlighted in bold and denoted with #, respectively.) For the abbreviations of the layers, see Figure 1 (44).

	PWR - 1 min			PWR - 5 min	
	r	***p***		**r**	***p***
GCL+IPL_I	-0.440	0.046 #	**GCL+IPL_T**	0.584	0.005 #
INL_ T	0.502	0.021 #	**GCL+IPL_I**	0.542	0.011 #
INL_I	0.553	0.009 #	**GCL+IPL_O**	0.481	0.027 #
CRC_C	0.472	0.031 #	**INL_C**	-0.668	**0.001**
CRC_O	0.501	0.021 #	**OPL_T**	-0.440	0.046 #
			CRC_O	-0.503	0.020 #

4.2. The assessment of retinal and choroidal changes following intensive physical exercise in senior elite athletes

4.2.1. Demographic characteristics of the study subjects

Seventeen eyes of 17 senior elite athletes (11 men and 6 women) were enrolled in the study. No otherwise eligible participants needed to be excluded during the study. Each participant declared to have performed regular intensive physical activity at least twice a week (mean 6.1 ± 2.8 hours/week) in the past 10 years. The mean duration of doing sports was 48.2 ± 18.3 years. Most study athletes regularly took part in national, European, and world championships at a senior level as well, with outstanding results. The demographic data of the study participants, namely age, gender, height, weight, BMI, SBP and DBP, HR, SE, BCDVA, and PWR are shown in Table 5.

Table 5. Descriptive statistics of the study participants. Body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP, respectively), heart rate (HR), spherical equivalent (SE), best-corrected distance visual acuity (BCDVA), power-to-weight ratio (PWR). Data are presented as means (SD) (45).

	Senior athletes (n=17)
Age (years)	67.9 (7.4)
Gender (m/f)	11/6
Height (m)	1.7 (0.1)
Weight (kg)	72.5 (13.2)
BMI (kg/m2)	23.7 (3.3)
SBP (mmHg)	131.2 (17.1)
DBP (mmHg)	80.9 (12.8)
HR (1/min)	71.5 (18.5)
SE (D)	+0.6 (1.1)
BCDVA (logMAR)	-0.1 (0.1)
PWR (W/kg)	1.7 (0.6)

4.2.2. Baseline thickness data of the different retinal layers and the choroid

The baseline thickness data of the single retinal layers, the composite layers, and the choroid are shown in Table 6.

Table 6. Layer thickness data of the senior athletes (n=17) for total thickness of the entire macula (T) in the central subfield (C), inner ring (I), and outer ring (O). The data are shown as means (SD). For the abbreviations, see Figure 1 (45).

	T	C	I	O
Single layers				
RNFL	37.1 (3.4)	15.3 (1.0)	26.6 (2.3)	41.0 (3.9)
GCL+IPL	71.3 (5.4)	40.6 (11.8)	93.2 (7.2)	65.9 (5.1)
INL	33.0 (2.2)	22.4 (5.5)	41.4 (3.6)	31.0 (2.2)
OPL	25.4 (2.2)	18.9 (2.9)	26.4 (2.1)	25.3 (2.6)
ONL+IS	75.3 (7.9)	118.3 (12.0)	88.7 (9.4)	69.7 (7.8)
ELZ+OS	34.7 (2.1)	33.2 (2.5)	33.5 (2.6)	35.2 (2.0)
IDZ+RPE	32.0 (3.1)	40.0 (4.4)	34.9 (3.7)	30.9 (2.9)
Composite layers				
GCC	108.4 (7.1)	55.9 (12.6)	119.9 (8.5)	107.0 (7.0)
PRL	110.0 (7.7)	151.4 (11.9)	122.2 (9.1)	104.9 (7.5)
OR	167.4 (9.0)	210.4 (12.4)	183.6 (10.4)	161.1 (9.1)
TR	308.9 (14.1)	288.7 (23.3)	344.8 (16.0)	299.0 (14.1)
Choroid				
CRC	252.0 (77.0)	279.0 (87.4)	272.0 (86.5)	245.1 (74.2)

4.2.3 Correlations between demographic characteristics and baseline layer thickness values

There was no significant correlation between demographic characteristics and baseline layer thicknesses, thus, height, weight, BMI, and gender had no effect on baseline thickness data. Age showed a trend toward positive correlation (missed

significant statistical values) with baseline RNFL in every region except in the central subfield, with ONL+IS and PRL in the center and OR and PRL in the inner ring.

Also, a trend toward positive correlation with a missed significance was observed between BCDVA and ONL+IS and also PRL in the center. Performance (power-to-weight ratio) showed a tendency towards negative correlation with RNFL in the outer ring, ELZ+OS in every region except in the outer ring. In contrast, a trend towards positive correlation was observed with the INL in the inner ring. Maximal heart rate seemed to negatively correlate with PRL in every region except the inner ring, similar to the ONL+IS in the outer ring and the total macula. Blood pressure had a trend towards a positive correlation with the OPL in the outer ring and the total macula. The above data are presented in Tables 7a and 7b.

Table 7a. Correlations between demographic characteristics and baseline single layer thickness values of senior athletes. The Pearson correlation coefficients with *p*-values below are denoted with # in case of a missed significant correlation. Only layers with at least one missed significant correlation are shown. Best-corrected distance visual acuity (BCDVA), power-to-weight ratio (PWR), heart rate (HR), and systolic blood pressure (SBP). For the abbreviation of the layers, see Figure 1. (45).

	Age		**BCDVA**		**PWR**		**HR**		**SBP**	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
RNFL_T	0.497	0.042 #	0.305	0.233	-0.463	0.061	-0.116	0.657	0.211	0.417
RNFL_I	0.496	0.043 #	0.341	0.18	-0.183	0.482	-0.298	0.245	0.091	0.730
RNFL_O	0.485	0.048 #	0.291	0.258	-0.498	0.042 #	-0.084	0.748	0.226	0.384
INL_I	-0.318	0.213	-0.139	0.594	0.488	0.047 #	-0.031	0.907	0.033	0.899
OPL_T	-0.026	0.922	0.072	0.784	-0.125	0.632	0.041	0.876	0.515	0.032 #
OPL_O	-0.073	0.78	0.052	0.842	-0.042	0.873	0.041	0.876	0.515	0.035 #
ONL+IS_T	0.318	0.213	0.170	0.513	0.030	0.909	-0.498	0.042 #	0.058	0.824
ONL+IS_C	0.541	0.025 #	0.495	0.043 #	0.089	0.735	-0.458	0.064	-0.054	0.836
ONL+IS_O	0.238	0.358	0.085	0.746	0.034	0.896	-0.497	0.042 #	0.064	0.783
ELZ+OS_T	0.096	0.713	0.280	0.276	-0.511	0.036 #	-0.132	0.614	0.420	0.093
ELZ+OS_C	0.068	0.795	0.074	0.779	-0.619	0.008 #	-0.107	0.682	0.374	0.139
ELZ+OS_ I	0.182	0.484	0.249	0.335	-0.560	0.019 #	-0.126	0.630	0.287	0.265

Table 7b. Correlations between demographic characteristics and baseline composite layer thickness values of senior athletes. The Pearson correlation coefficients with *p*-values below are denoted with # in case of a missed significant correlation. Only layers with at least one missed significant correlation are shown. Best-corrected distance visual acuity (BCDVA), power-to-weight ratio (PWR), heart rate (HR), systolic blood pressure (SBP). For the abbreviation of the layers see Figure 1. (45).

	Age		**BCDVA**		**PWR**		**HR**		**SBP**	
	r	***p***	**r**	***p***	**r**	***p***	**r**	***p***	**r**	***p***
PRL_T	0.353	0.165	0.251	0.331	-0.109	0.678	-0.546	0.023 #	0.174	0.503
PRL_C	0.561	0.019 #	0.516	0.034 #	-0.041	0.875	-0.486	0.048 #	0.024	0.927
PRL_I	0.523	0.031 #	0.412	0.100	-0.157	0.547	-0.476	0.053	0.112	0.670
PRL_O	0.260	0.313	0.164	0.528	-0.089	0.733	-0.545	0.024 #	0.196	0.451
OR_I	0.510	0.037 #	0.405	0.107	-0.102	0.698	-0.375	0.138	0.220	0.397

4.2.4. Postexercise thickness changes of chorioretinal layers

A significant thinning of the total retina was observed 1 minute post-exercise (-1.6 ± 1.1 µm, p <0.001) which was followed by a trend towards thickening at 5 minutes with missed significance (1.5 ± 1.0 µm, p <0.05). By 30 minutes the total retinal thickness approached the baseline. These changes were significant in the inner and outer ring, as well with thinning at 1 minute (-1.7 ± 1.2 µm, p =0.001, -1.5 ± 1.2 µm, p <0.001) followed by a missed significant thickening at 5 minutes (+1.1 ± 1.1 µm, p <0.05, +1.0 ± 1.1 µm, p <0.05, respectively). In the central subfield, the thickening was only significant at 5 minutes (1.5 ± 1.1 µm, p <0.05; Figure 7).

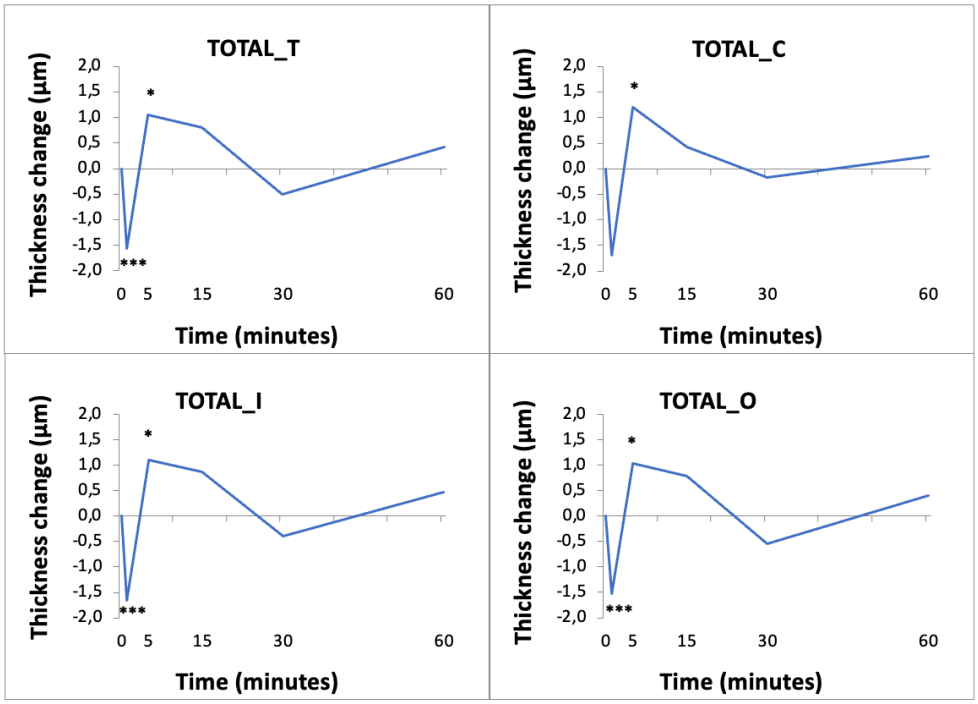

Figure 7. Changes of total retinal thickness (TR) of senior athletes over time following cycle ergometer strain. Data are shown in the total macular area (T), the central subfield (C), the inner (I) and outer ring (O). *: p <0.05 (missed significance), ***: p <0.001 (significant) (45).

This trend above was present in all single retinal layers, but significant changes were detected only in the GCL+IPL layer complex at 1 minute with missed significance at 5 minutes (-0.4 ± 0.4 µm, p <0.001 and +0.2 ± 0.1 µm, p <0.05, respectively) in the outer ring. See Figure 8.

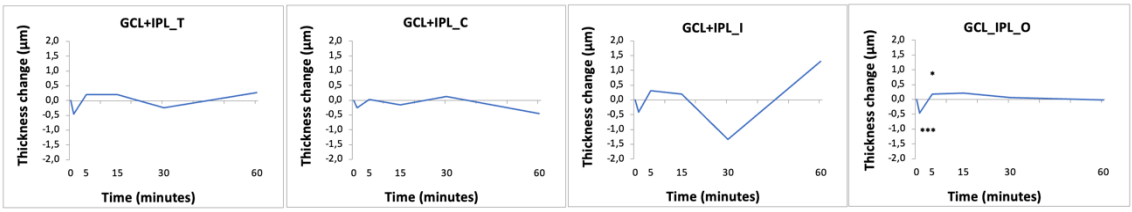

Figure 8. Changes of the GCL+IPL layer thickness over time following vita maxima strain of senior athletes. Only the GCL+IPL composite layer showed significant alterations as presented in this figure. Data are shown in the total macular area (T), the central subfield (C), the inner (I), and outer ring (O). *: p <0.05 (missed significance), ***: p <0.001 (significant). (45).

Among the composite layers, no significant changes were observed. The trend observed in the case of the total retina has also appeared in the composite layers; however, the changes were not statistically significant. Missed significant results were found at minute 1 for the GCC in the outer ring (r =-0.704, *p* =0.035) and at minute 5 for the OR in the entire macula and the outer ring (r =0.829, *p* =0.023; r =0.724, *p* =0.031, respectively).

There was no significant change in choroidal thickness; however, we could detect a tendency towards thinning at 1- and 5-minutes post-exercise, which was followed by a thinning at 15 minutes and then a slight thinning which was kept on after 60 minutes. This trend was observed in every region but the central subfield, where after a thickening at 1 minute and thinning at 5 minutes, an overcompensated thickening was detected at 15 minutes which was followed by a slow decrease (Figure 9). The absolute changes in choroidal thickness did not show any correlation with the thickness changes of the intraretinal layers.

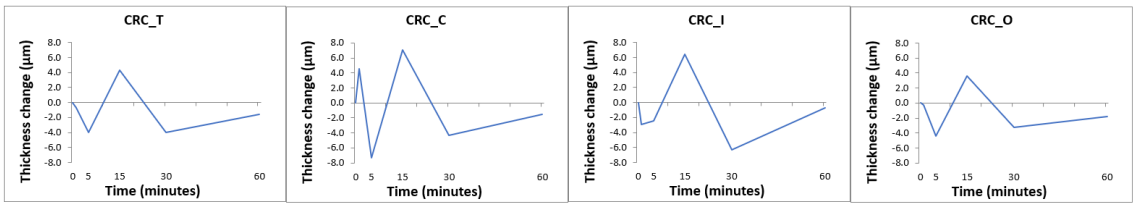

Figure 9. Changes observed in the choroid (CRC) of senior athletes over time following cycle ergometer strain. The changes were not statistically significant (from left to right, entire macula, central subfield, inner and outer rings) (45).

4.1.5. Confounding factors

No significant correlation was observed between the layer thickness changes from baseline to minute 1 and minute 5 measurements and the PWR. Missed significant correlations were found at minute 1 for the RNFL in the outer ring and INL in the inner ring (r =-0.527, *p* =0.032 and r =0.556 and *p* =0.025) and at minute 5 for the INL and OPL in the inner ring and ELZ+IS in the central subfield (r =0.596, *p* =0.012; r =-0.562, *p* =0.019; r =-0.580, *p* =0.015, respectively).

5. DISCUSSION

Physical inactivity substantially impairs an individual's health, leading to muscle mass and strength decline, cardiorespiratory fitness reduction, cardiovascular or metabolic diseases, and thereby poses a huge burden on societies worldwide. A growing body of evidence indicates that regular physical activity has a favorable impact on health and physiology. Beyond its obvious beneficial effect on body weight, blood pressure, inflammatory processes, and neuroprotection (9-13, 15, 16), it is furthermore supposed to have an independent impact on reducing cardiovascular risk (6). Therefore, being engaged in sport activities may act as a medicine in certain conditions, leading to an increase in life expectancy by reducing mortality (5), and thus have a significant epidemiological impact on society (4).

The recently introduced concept of frailty in older adults encompasses their fitness level, endurance, strength, and physical functions. As the word “frailty” was widely used to describe the loss of energy, physical ability, cognition, health that can rise the level of vulnerability. The term has been clarified by Rockwood et al in the second clinical investigation of the Canadian Study of Health and Aging (47). Besides reduced physical activity, age, gender, poor oral hygiene, diabetes, chronic kidney disease, and depressive symptoms are risk factors for frailty (48). According to the 2014 Frailty Consensus, however, frailty can be substantially reduced by increasing protein and vitamin D intake, minimizing medication use, and by promoting physical activity, thereby reducing the incidence of chronic diseases and extending the lifespan (49). It is important to note that visual impairment due to cataracts, glaucoma, or AMD is also known to increase frailty (50-53).

In addition to the "classic" steady-paced activities, high-intensity interval training, generally referred to as HIIT has gained popularity over the past few years. HIIT is characterized by alternating short intense anaerobic exercises and short regeneration periods until exhaustion. HIIT has approximately the same effect on aerobic capacity, glycemic control, and muscle mass as previous training methods, but in half the training time. Although being shorter, it significantly increases fitness, and significantly reduces mental anxiety and depression (54).

Acute systemic physiological changes caused by physical activity enable stable blood flow in different organs even in extreme conditions. The elevation in blood pressure and pulse rate helps the nutrition of musculoskeletal tissues by improving the transport of blood and oxygen (55, 56). In addition, redistribution of the blood flow is supported by vasoconstriction in the capillaries that take place throughout the rest of the body as a result of stress hormones provoked by physical activity (57). Similarly to the autoregulation mechanism detected in the brain, the retina also has its own remarkable ability to provide a continuous and sufficient blood flow. Recent evidence indicates that smaller vessels within the retina play an important role in regulating the blood flow in this tissue. Furthermore, even little alterations in arterial blood pressure pose the potential to have an impact on the rheological properties of the retina (58-60). This alteration may result in macular and peripheral blood flow differences. On the other hand, choroidal vasculature is predominantly composed of blood vessels with an intense blood flow that nourishes the outer retina and cools photoreceptors that generate excessive heat during light signal processing (61). Based on studies conducted on healthy volunteers, moderate physical activity leads to an increased blood flow in the choroid whereas the retina does not show a similar increase in blood flow due to retinal autoregulation (62-66). Nevertheless, there is evidence supporting the existence of choroidal autoregulation, as well (12, 67).

Due to the fact, that alterations of the vascular system and factors associated with the cardiovascular might influence many ocular pathologies, the incidence of these diseases, such as AMD, glaucoma, cataracts, or diabetic retinopathy, dramatically increases with increasing age (68). The amount of information concerning the immediate and direct effects of physical exertion on the retina and choroid is relatively limited. However, earlier studies indicate that regular physical exercise has a beneficial impact in reducing the probability of these conditions and slowing their progression (25, 68-70).

Therefore, in our clinical studies, we evaluated the acute chorioretinal morphological alterations due to short intense physical exercise in physically active young adults with different fitness levels and senior athletes. In addition, we examined the possible differences in young and older adults using our custom-built OCT image processing tool to detect structural changes in SD-OCT images.

In young sportsmen, undergoing *vita maxima* strain, we revealed an acute thinning of the retina at 1 minute, which was followed by an immediately observable transient

thickening of the retina by 5 minutes post-exercise. This increased thickness persisted until full restoration to baseline levels was achieved within 30 minutes. The observed alteration appeared particularly in the granular layers of the retina and did not show any correlation with exercise performance. Furthermore, this change seemed to be unaffected by the individual's professional or amateur status. It could be hypothesized that alterations in the choroid might be responsible for the rapid changes observed in the outer retina. On the other hand, there was no discernible pattern in the choroidal thickness changes, and additionally, no association was found between thickness changes in the retina and the choroid. The identified changes in the choroidal thickness were not as we expected them initially, characterized by rapid structural changes by first getting thinner and then immediately thickening, followed by sustained thinning; nevertheless, these findings were not below the preset threshold for significance. The explanation of these observations is ambiguous as the examination of alterations in the choroid after physical exercise has been a subject of ongoing debate within the scientific community (66, 71-76).

Our results in senior athletes completing an age-matched *vita maxima* strain also indicate a similar acute response in the retina: we observed an immediate thinning that was followed by a significant thickening at the 5 minute measurement. After this, thickness gradually returned to baseline. This trend also appeared in the three nuclear retinal layers, at most present in the outer retina. Despite the clearly observable trend, there were no statistically significant changes observed by the layer analysis. Similarly to the observations in young adults, alterations of the retina and choroid failed to show any association following exercise. Furthermore, no discernible tendency was observable in the thickness changes of the choroid which may be attributed to the high variability in measurement.

What could be the physiological mechanisms behind our observations? The myogenic response of the blood vessel wall is the primary mechanism that is responsible for the autoregulation of the retina. Namely, in response to an elevation in transmural pressure caused by the variations in BP, vasoconstriction develops in the small arteries and arterioles (59). In contrast, a reduction in internal pressure leads to the dilation of blood vessels (59), which is consistent with our observations around 5 minutes after exercise, when the restitution process begins with a drop in BP and a loss of

vasoconstriction dominance, resulting in a rebound thickening of the layers above. This BP-driven alteration in the retina has been demonstrated *in vivo* (58-60), where an increase of approximately 20 mmHg in SBP resulted in responsive vasoconstriction. This physiological response is considered to be influenced by endothelial cells and many local mediators, including oxygen, carbon dioxide, angiotensin-II, adenosine, nitric oxide, and endothelin-1 (77). In previous investigations conducted by young adults, OCT-angiography has been employed to reveal variations in macular vessels. According to these results, physical activity reduces the vascular density of macula (76, 78, 79). Interestingly, in the case of greater aerobic exercise capacity, reduced FAZ regions have been found suggesting exercise-induced adaptation in the retina (80).

As no vascular element exists in the outer retina, our observation of an initial thinning with the subsequent thickness increase of the ONL+IS and IDZ+RPE composites in our subjects is most likely due to either a metabolic or a biomechanical change. After physical exertion, Vera *et al.* observed an acute IOP peak that subsided within five minutes in trained participants and took somewhat longer in untrained ones (81). Thus, such an IOP peak may in turn result in a mechanically exerted compressive effect on the retina, which includes the photoreceptor and RPE layers. The plausibility of the hypothesis of mechanical compressions could be supported by considering that layers, that contain the cell nuclei, may be altered while the axonal layers remain largely unaffected. This might be due to the fact that the cell bodies can undergo more volume changes compared to the layers comprising axonal structures (such as the RNFL, IPL, and OPL).

From another point of view, recent findings on hyperbaric changes suggest that metabolic factors might also contribute to the observed phenomena with the transient shortening of the photoreceptors that could serve as an explanation for our observations (82). Moreover, findings from experiments conducted on mice suggest that hypoxia may also lead to a reduction in the length of photoreceptor outer segments, thus, accounting for the observed length reduction in the outer retina. A metabolic shift in such a short time, however, seems rather unlikely (82).

Several factors may have contributed to the somewhat distinct acute responses of young and senior athletes to intense physical exercise in our assessments. First, the strain methodologies used in the two studies were marginally different. To assure

cardiovascular safety, older individuals followed the Maffetone formula of (180 – age) beats per minute for maximal HR. This may have affected the significantly higher power values in young adults, culminating in a decreased sympathetic answer to exercise in senior sportsmen.

Second, assuming the alterations in IOP during exercise may contribute to the observed acute thinning at 1 minute (either independently or in conjunction with the vasogenic response), it might be hypothesized that short-term physical strain in the senior population is leading to a smaller increase in intraocular pressure.

Age-related variations in the dynamics of the retinal microvasculature could be a third potential explanation for the disparities in retinal response between our cohorts of young and older adults. Previous studies have suggested that an increased augmentation index, caused by the thickening of the arterial wall, may lead to a reduced responsivity of the retinal vessels that could be present in our senior cohort, as well (83, 84). This can also be supported by the observation of Seshadri *et al*., who investigated the retinal vascular response after flicker light stimulation in different healthy age groups and found decreased retinal vasoconstriction along with a reduced arterial dilatation amplitude in older adults, compared to younger or middle-aged people (84). According to Hartog *et al*., aortic wall stiffness and wall thickness seem to be associated with a more pronounced elevation in blood pressure following isometric challenges in older individuals compared to young adults (85).

Our studies could not identify any significant association between alterations in retinal and choroidal thickness following exercise. Furthermore, the choroid did not exhibit a discernible pattern of changes, possibly due to the substantial variability in the measurements. In myopic eyes, some studies have reported a notable reduction in macular and optic nerve head flow density, as well as a decrease in vascular density in the deep retinal layers after exercise (71). Additionally, increased vascular density was observed in the entire retina of both myopic and emmetropic children after a 30-minute period of rest following physical exercise (74). These data may provide an explanation for the observed tendency of a significant retinal thickness reduction following exercise in our study population.

Nevertheless, the correlation between choroidal response and physical strain remains an issue of debate, as indicated by previous research findings. Li *et al*. observed

a thinning in choroidal thickness in pediatric individuals after at least 30 minutes of moderate exercise (74). It is important to note, however, that the first 10 minutes of the recovery period were not included in the monitoring process. On the other hand, Sayin *et al.* reported that subfoveal choroidal thickness increased within 5 minutes after a 10-minute low-impact, moderate-intensity exercise which was followed by a full recovery to baseline values by 15 minutes post-exercise; however, the retina did not show any thickness change (66). Contrary to the above, a study involving 60-year-old healthy adults found that physical activity resulted in an increase in SBP, but there were no statistically significant changes identified in choroidal thickness as measured by SD-OCT (72). In a different investigation in healthy individuals between 40 ± 10 years of age, no alterations were observed in the thickness of the choroid within the first 10 minutes after mild dynamic physical strain (86), causing increased BP, HR, and mean ocular perfusion pressure.

Blood flow in the choroid may be modulated by its vascular and non-vascular smooth muscles, due to their dilatation or constriction (73). Thus, in response to the modification of the IOP, the sympathetic innervation of the capillaries may activate the autoregulation of the choroid (61). Choroidal autoregulation, on the other hand, remains a matter of controversy. Whereas a 97.5%, increase in perfusion pressure did not affect the choroidal circulation in healthy individuals, a 23% elevation in perfusion pressure is enough to increase the choroidal flow in AMD patients (75). In another setting, comparing healthy persons to those diagnosed with open-angle glaucoma, a reduction has been revealed in choroidal blood flow assessed by confocal laser Doppler flowmeter before and after a physical effort. Following exercise, the observed increase in perfusion was found to be two times higher in study participants with glaucoma compared to healthy controls (87).

Overall, the reaction of the choroid to physical stress remains controversial and may be influenced by various factors, including age, refractive error, exercise intensity, and individual variations in vascular regulation. Further investigation is needed to clarify the mechanisms underlying the choroidal response to exercise and its potential consequences for ocular health.

In light of the above, the question arises of how physical activity can exert its preventive effects in reducing the incidence of ophthalmic diseases, particularly retinal

pathologies. First, regular physical activity could maintain the health of the vascular system by decreasing systemic inflammation, and endothelial dysfunction (9) and preventing the development of arterial stiffness by reducing oxidative stress (6).

Another possible mechanism could be the neuroprotective effect of physical activity. The significance of brain-derived neurotrophic factor (BDNF), as demonstrated by Boatright *et al*., seems to become evident in the context of exercise-mediated retinal neuroprotection (88). In the animal studies mentioned in the introduction, mild treadmill training has been shown to reduce degenerative changes in the retina induced by toxic light in mice; the reduction in inner nuclear layer apoptosis has also been described in diabetic rats (17, 19). Swimming could prevent ganglion cell apoptosis in a mouse model of glaucoma (18). Treadmill workout has been found to have a potential preventive effect on photoreceptor degeneration in models of inherited photoreceptor dystrophies (89). In the aforementioned studies, BDNF levels were higher in the trained animals, while the protective effect was reversed by the administration of a systemic BDNF receptor antagonist (17).

Ultimately, increased choroidal blood flow resulting from even moderate physical activity (62, 65, 66) may assist in maintaining the health of the photoreceptors and the RPE not only by supplying the outer retina, but with cooling the photoreceptors that generate a large amount of heat during light signal processing (61). Furthermore, the increased perfusion of the optic nerve head and the macula due to regular exercise may have an additional cytoprotective effect on the inner retina (90).

A critical evaluation of the limitations inherent in our research is essential. Initially, a relatively small number of participants were enrolled, particularly when comparing young professionals to amateurs. A larger number of participants would be necessary to obtain a more accurate assessment of the association between retinal and choroidal parameters with subjects' characteristics, such as age, SE, height, weight, BMI, DBP, and HR. However, it is important to note that our study was rather aimed as an exploratory, pilot investigation upon which future studies can be built. Second, within the framework of cooperation with the University of Physical Education in Budapest, the young and senior elite athletes, who were enrolled in these studies, went through a routine control at the Department of Health Sciences and Sports Medicine of the University. Due to a well-trained cardiovascular system and the minimal or no presence of comorbidities,

it is possible that the responses of our participants to the applied load were different compared to those of an age-related control group which is expected to have more severe diseases. Third, for technical reasons, axial length data are not available, which could have influenced the segmentation values (91). However, we consider that our methodology assessing layer thickness alterations compared to the baseline data, instead of simply using the actual thickness of the layers, helped to mitigate potential biases. Fourth, as mentioned previously, intraocular pressure might have influenced our results (81); however, performing applanation or non-contact tonometry alongside OCT imaging during and after the physical strain would have been technically challenging, particularly at the beginning of the recovery period, within the first 5 minutes whereas the equipment in our lab did not include an applanation tonometer. In addition, a shortage of sleep and caffeine intake both also have the ability to potentially influence the physiological functions of the eye. On the day of the trial, participants were instructed to refrain from consuming coffee, but their sleep habits were not assessed. It needs to be noted that we implemented an age-matched *vita maxima* type exercise in our study population. This exercise program consisted of gradually increasing the intensity until participants attained a state of exhaustion or achieved their maximum physiological age-related HR or a peak in SBP representing a highly demanding load. Still, the senior athletes were not subjected to the peak strain but rather a sub-maximal exertion, in order to prioritize their safety.

Last but not least, we used a custom-built, semi-automatic algorithm for the segmentation of OCT images. In the meantime, there are deep learning-based tools available for the same task that offer highly precise segmentation in a fraction of the time needed with OCTRIMA (92-98). We could show a high reproducibility of our algorithm previously in retinae lacking pathological changes, such as in our study settings (31). Therefore, we believe our layer thickness data are precise, and our results are reliable. Also, at the time we conducted our studies, these modern tools were not publicly available.

To the best of our current knowledge, this work represents first the rapid alterations in the retinal and choroidal morphology as consequences of vigorous physical exertion in both young and older adults. We believe our work provides valuable insights into the acute alterations of retinal structure following physical exercise in well-trained young and older individuals. Notably, we observed an initial transient thinning followed

by thickening of the granular layers of the retina, with complete restitution within 30 minutes post-exercise. Though the exact reasons for these changes remain unclear, they could possibly explain the phenomenon of blackouts reported by professional sportsmen during intense physical exertion. We hypothesize that a combination of acute stress-related vascular alterations of the inner retina, and biomechanical changes of the outer retina following IOP increase might underlie these changes. The choroid, on the other hand, neither seems to play a significant role in these changes, nor it show any acute alterations due to heavy physical strain, suggesting that physiological processes maintain constant morphological parameters under such conditions.

The relevance of our results in a practical context is currently not entirely certain. We suppose, that the immediate retinal responses triggered by physical activity and regular exercise might potentially have a considerable impact on providing eye health. This theory may propose long-term the possibility of an entity analogous to the concept of the "trained heart" in cardiology, which we provisionally define as the "trained eye" referred to (99). Nonetheless, further investigation is necessary, particularly in a larger and prospective cohort comprising non-trained participants, including those affected by age-related retinal diseases. This investigation might offer a better understanding of the underlying mechanism of such non-communicable eye diseases as AMD, diabetic retinopathy, macular edema, and glaucoma. These conditions are becoming more prevalent in our aging societies. While there is emerging evidence that regular physical exercise may operate as a preventive factor against many illnesses, the specific processes are unknown. While a growing number of evidence suggests that regular physical activity might act as a protective factor against these conditions, the precise mechanisms remain unclear.

The outcomes of our study and the methodology we employed might potentially help the deeper understanding of the ocular pathologies and their relationship with physical exercise. Furthermore, our findings could possibly operate as a catalyst in the development of recommendations that advocate for an active and health-conscious lifestyle, with a particular emphasis on promoting visual well-being.

6. CONCLUSION

In our work, we assessed the immediate changes in the retina and choroid due to acute high-intensity physical exercise using SD-OCT imaging in both young and senior athletes with distinct fitness levels.

We found in our cohort of young adults (18–35 years of age) that professional athletes have thicker retinas and choroids compared to those of amateur sportsmen; nonetheless, statistically significant distinction existed solely within the choroid in every region (in the total macula, central subfield, inner ring, and outer ring), along with the RNFL and PRL in the central subfield.

Our research revealed that undergoing *vita maxima* strain, the retina of the young adults presented an obvious pattern of response. By 1 minute of recovery, there was a noticeable reduction in retinal thickness, followed by a marked thickening response within 5 minutes post-exercise endured until a full return to the baseline conditions occurred within a relatively short period of 30 minutes. Our results indicate that these changes were most pronounced in the granular layers of the retina. The reasons behind this phenomenon are rather unclear, it could be related to IOP changes, hypocapnia, or choroidal changes. Further studies are warranted to investigate our observations.

Senior athletes (over 50 years of age) performing an age-matched vita maxima strain demonstrated a similar acute retinal response to young adults, with thinning at 1 minute, followed by an almost immediate thickening within five minutes, which gradually normalized over time. This trend appeared mainly in the outer part of the retina; although these changes did not achieve a statistically significant level according to the segmentation data.

Analogously to the observations in young adults, our research did not reveal significant changes in the choroid, and there was no correlation between changes in retinal and choroidal thickness following exercise in senior athletes. This suggests that the choroid, despite its anatomical proximity to the retina, may not play a significant role in immediate physiological adjustments during exercise, at least in terms of thickness.

Furthermore, we also demonstrated that the observed retinal alterations appeared to be unaffected by whether someone was a professional or engaging in exercise at an amateur level. Moreover, these alterations did not exhibit any clear connection with exercise performance, both in the young and the senior athletes.

7. SUMMARY

According to current evidence, regular physical activity appears to have several beneficial effects on the retina, choroid, and visual function, effectively counterbalancing the detrimental consequences associated with a sedentary lifestyle.

The primary focus of our research was on the immediate chorioretinal changes after intense physical exercise. Our results revealed immediate alterations within the granular layers of the retina characterized by an initial thinning followed by rebound thickening and full recovery within 30 minutes. Notably, these changes were less expressed in older subjects in comparison to young adults, but they were inarguably visible as a trend.

Interestingly, the choroid, which plays an important role in outer retinal physiology, appeared not to be involved in these changes, as it showed no immediate response during intense physical strain. This result also implies that fundamental physiological mechanisms are at play in the choroid, maintaining consistent morphological parameters even under extreme physiological conditions.

We hypothesize that a combination of acute stress-induced vascular changes in the inner part of the retina coupled with biomechanical effects on the outer retina as a consequence of increased intraocular pressure (IOP) and metabolic mechanisms might underlie these effects.

The combination of our findings in both young and older adults could provide valuable insights into the mechanisms of how physical exercise can influence the retinal pathophysiology of several retinal disorders, a matter of growing significance given the aging demographics of our societies.

We hope that our findings will encourage the development of guidelines promoting an active lifestyle to preserve eye health. Furthermore, our results could potentially facilitate the implementation of tailored preventive care strategies, ensuring individualized attention to eye health preservation and thus reducing the individual and social burden of non-communicable eye diseases.

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