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Research Paper

Morphological changes in retinochoroidal microvasculature after caffeinated versus decaffeinated coffee consumption☆

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ABSTRACT

Background: To investigate changes in retinochoroidal microvascular morphology after caffeinated versus decaffeinated coffee consumption in age- and gender-matched healthy individuals using optical coherence tomography (OCT) and OCT angiography (OCTA).

Methods: In this prospective, randomized clinical study, a staff member in charge of record keeping randomly assigned 48 healthy volunteers to two groups: caffeinated coffee consumers (24 eyes) and decaffeinated coffee consumers (24 eyes). Participants' ages and genders were recorded before consumption, and a comprehensive ophthalmologic exam was performed, followed by OCT and OCTA analyses before, 30 min, one, six, and 24 h after blindly consuming either of the coffees.

Results: Caffeinated and decaffeinated coffee consumers had mean ages of 23.45 ± 0.92 and 22.73 ± 1.13, respectively ($p = 0.407$). The following parameters changed significantly in caffeinated coffee consumers 30 min and 1 h post-consumption (pre-consumption versus 30 min versus one hour post-consumption; $p < 0.05$): a) parafoveal superficial capillary plexus vessel density (%): 54.45 versus 51.8 versus 51.92, b) parafoveal deep capillary plexus vessel density (%): 55.16 versus 52.45 versus 52.83, c) outer retinal flow area (%): 8.87 ± 1.91 versus 8.03 ± 1.88 versus 8.11 ± 1.93, d) choriocapillaris flow area (mm^2): 20.95 ± 0.98 versus 19.82 ± 1.20 a versus 19.62 ± 0.95, and e) sub-foveal choroidal thickness (μm): 295.06 ± 5.45 versus 277.08 ± 5.33 versus 260.71 ± 58.61. No significant differences in any OCT and OCTA parameters were found between consecutive measurements in decaffeinated coffee consumers ($p > 0.05$).

Conclusions: Caffeinated coffee appears to transiently reduce parafoveal vessel density, capillary flow area, and sub-foveal choroidal thickness. Lack of these microvascular morphological changes in decaffeinated coffee suggests a potential caffeine-induced vasoconstrictive effect.

1. Introduction

Coffee is one of the most consumed caffeinated drinks in the world [1]. Its popularity is largely due to its caffeine content, which ranges from 30 to 175 mg per cup of coffee [2]. In addition to caffeine, coffee consists of chlorogenic acids, diterpenes, cafestol, and kahweol. Cooked coffee with many of these ingredients is a complex mixture of anti-oxidant, anti-inflammatory and anti-fibrotic properties which provide scientific evidence for epidemiological study correlations [3–7]. Recent studies have demonstrated the effects of caffeine on the cardiovascular system, in addition to its stimulating effects on the central nervous system [8]. It has also been shown to have a vasoconstrictive effect on the ocular microvasculature, not only directly through constriction of the retinal arterioles [9], but also indirectly through an increased resistive index of the ophthalmic, central retinal and short posterior ciliary arteries [10]. Caffeine consumption varies according to country and ethnicity throughout all age categories [2]. It is used as a neuro-stimulant globally, and is clearly beneficial at normal doses described as daily consumption ranging from 200 to 300 mg [11]. In high doses, on the other hand, it may cause irregular conditions, so patients taking anxiolytic medications should avoid or significantly reduce their caffeine consumption. In this circumstance, patients may be given decaffeinated instead of caffeinated coffee to help them consume less caffeine [12]. Nonetheless, caffeine-free drinks, while known to be

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minimal, are also known to contain varying levels of caffeine.

Retinal microvasculature consists of the central retinal artery, which branches into four major intraretinal arteries that extend toward the peripheral retina and feed into a capillary bed. Retinal venous system is structured similarly, with the central retinal venule draining into the cavernous sinus. Retinal capillaries form a two-layer network that is interconnected. Superficial capillary plexus (SCP) is a microvascular system in the nerve fiber and ganglion cell layers that contains arterioles, venules, and capillaries. Deep capillary plexus (DCP) is a second microvascular system that lies deeper in the inner nuclear and outer plexiform layers, and is primarily composed of capillary-sized vessels [13]. Because of the retinal thinness in the avascular fovea, adequate retinal oxygenation is possible through choroidal circulation [14].

The most vascularized ocular tissue, the retinochoroidal layer, plays an important role in the pathophysiology of many ocular diseases [15]. Observing retinochoroidal microvascular morphological changes is therefore crucial. Yet, quantifying the retinochoroidal microvascular morphology has been extremely difficult due to limited resolution and repeatability of traditional imaging modalities. We now have a much better understanding of the retinochoroidal layer thanks to advancements in enhanced depth imaging optical coherence tomography (EDI-OCT) [16]. Moreover, OCT angiography (OCTA) is a novel non-invasive technology that employs motion contrast imaging to produce angiographic images in seconds using high-resolution volumetric blood flow data. It generates volumetric data with the clinical potential of precisely localizing and pinpointing disease, as well as revealing functional and ultrastructural details simultaneously.

Caffeinated coffee should be given special consideration since it is not just the main source of dietary caffeine, but also the most popular beverage on a global scale [17]. Despite this, there have recently been few, if any, quantitative studies, the majority of which have investigated the acute effects of caffeine on macular microcirculation using OCTA with varying results. Thus, the current study aimed to investigate changes in retinochoroidal microvascular morphology after caffeinated versus decaffeinated coffee consumption in age- and gender-matched healthy individuals using EDI-OCT and OCTA.

2. Materials and methods

2.1. Study design and participants

In this prospective, randomized, single-centered clinical study, 48 healthy Turkish descent volunteers were randomly divided into two groups: caffeinated and decaffeinated coffee consumers. A staff member in charge of record keeping led the participant into a room and designated him or her a random number to a separate group. The study protocol complied with the ethical principles of the Declaration of Helsinki and received full approval from the institutional review boards of Afyonkarahisar Health Sciences University Ethics Committee (2011-KAEK-2, Acceptance code: 2019/7–162). Prior to the study, all participants issued informed written consent

2.2. Inclusion and exclusion requirements

None of the healthy participants, who were recruited from hospital personnel and their spouses, consumed coffee on a regular basis. Participants with the following characteristics were excluded from the study: (a) ocular disorders such as lenticulo-corneal opacities, glaucoma, nystagmus, congenital and/or acquired retinal diseases, (b) a history of ocular trauma or surgery, including anterior segment laser therapy, (c) migraine, (d) epilepsy, (e) pregnancy and/or breast-feeding condition, (f) any systemic disease, that is, heart disease, diabetes mellitus, anemia, etc., which could impair the ocular microcirculation, (g) a history of any chronic drug use (antihistamines decongestants, analgesics, sildenafil, etc.), (h) smoking habit, and (i) a possible tolerance to caffeine, defined as drinking >1 cup of coffee per day.

2.3. Preliminary ophthalmologic assessment

Before consumption, the participants' age and gender were recorded, and a comprehensive ophthalmologic exam was performed, including measurements of best-corrected visual acuity (logarithm of the minimum angle of resolution (logMAR), mean of the three intraocular pressures (IOP) (Goldmann; Haag-Streit AG, Köniz, Switzerland), and axial length (AL-Scan, Nidek CO., Gamagori, Japan), as well as slit-lamp biomicroscopy before and after artificial mydriasis with tropicamide 1% and phenylephrine 10%.

Two grams of caffeinated coffee equals about two cups of regular brewed coffee [18], which contains the average amount of caffeine consumed per day by a person in Western cultures [11]. In the current study, 2 gs of instant caffeinated or ground decaffeinated Turkish coffee were placed in 200 ml of 95 °C natural spring water that was free of sugar and other additives. Another non-study participant mixed the coffees in a completely separate kitchen for 30 s in a standardized manner while maintaining the randomization order. Following that, coffee was poured into separate standard 100-mL cups (approximately 65–100 mg caffeine) and bearing only the participants' initials. Participants who were unaware of the type of coffee they were drinking were given either type of prepared coffee and instructed to consume it within 5 min while observed. Caffeine-containing beverages, foods (chocolates), and/or drugs were not permitted during the study. Besides, exercise was restricted during the study because it could have an effect on the retinochoroidal microcirculatory system. Participant self-reporting was used to ensure that these requirements were met. To avoid diurnal fluctuations, both OCT and OCTA scanning procedures were carried out at the same time of day (9:00–11:00 a.m.) after at least 8 h of fasting. This involved measurements taken before, as well as 30 min, one, six, and 24 h after consumption.

2.4. Enhanced depth imaging optical coherence tomography

EDI-OCT scanning (Spectralis SD-OCT; Heidelberg Engineering, Heidelberg, Germany) was performed as described previously [16]. A single masked trained technician performed the scanning procedure with a dilated pupil while the video image of the central retina was monitored. The point of greatest depression within a 500-μm radius was designated as the foveal center [19]. The central macular thickness was defined as the distance between vitreoretinal interface and anterior surface of the retinal pigment epithelium to denote average macular thickness in the central 1 μm. The retinal nerve fiber layer thickness was determined by the number of pixels between the highly reflective layer at the vitreous surface and the points on each scan whose reflectivity exceeded a predetermined threshold. The retinal nerve fiber layer thickness protocol consisted of three 3.4 mm diameter circular peripapillary scans of the optic disk, each with 256 circumference measurements. The mean peripapillary retinal nerve fiber layer thickness was investigated after automatic measurement with a device's built-in software. In addition, all EDI-OCT images were blindly classified and delineated by two experienced ophthalmologists (MD & HHG) according to the proposed protocol. The sub-foveal choroidal thickness (SFCT) was determined using a measuring tool with a built-in linear measuring as the vertical distance from the outer surface of the hyper-reflective line denoting the retinal pigment epithelium and Bruch's membrane complex to the hypo-reflective line denoting the sclero-choroidal interface centered on the fovea. The mean SFCT was calculated by averaging two blind ophthalmologists' manual choroidal thickness measurements at the fovea, as well as 1500 and 3000 μm nasal and temporal distances from the foveal center.

2.5. Optical coherence tomography angiography

All OCTA (Optovue, Inc., Fremont, California, USA) procedures were also carried out by the same technician, who used the same device in

Angio Retina mode with a 6 × 6 mm scanning area. This system relies on the split-spectrum amplitude-decorrelation angiography algorithm, with blood flow serving as intrinsic contrast. This flow is defined as a time-dependent speckle pattern alteration caused by light scattered from erythrocytes and neighboring tissue interference. Using an 840 nm light source and an axial resolution of 5 mm, OCTA can generate volumetric scans of 304 × 304 A-scans at 70,000 A-scans per second. Ocular motion artifacts were minimized by eye-tracking and corrected by motion correction technology. The cut-off value for the image quality index was set at 8/10, with poor-quality scans excluded from the study. AngioVue Analytics (version 2017.1.0.155), an integrated software for quantitative analysis, was used to automatically measure vessel density (VD) and flow area. A 6 × 6 mm macular angiogram of the foveal, parafoveal, perifoveal SCP and DCP was used to determine the retinal capillary VDs. This was quantified by taking into account the percentage of pixels in the selected region that were covered by vessels and microvasculature. The SCP OCTA image was separated with an inner boundary 3 μm beneath the internal limiting membrane and an outer boundary 16 μm beneath the inner plexiform layer (IPL), whereas the DCP OCTA image was separated from 16 μm to 70 μm beneath the IPL.

The foveal avascular zone (FAZ) is a significant region bereft of flow signal on an en face macular angiogram that was automatically analyzed using OCTA FAZ mode software to determine parameters such as FAZ area, FAZ perimeter, and foveal VD in a 300-μm wide region around FAZ (FD-300).

The outer retina was located 70 μm beneath the IPL and 30 μm beneath the retinal pigment epithelium. The flow area was determined automatically by AngioVue software as the percentage of vessel area covered in a 2.97 mm-circle diameter in a selected area centered on the FAZ. The choriocapillaris layer was located between the retinal pigment epithelium and the deeper layer, with the retinal pigment epithelium offset of 31 μm and 59 μm, respectively [20]. The choriocapillaris flow area was calculated automatically by dividing choriocapillaris vessel areas by the selected areas using Optovue software with a flow function. Consecutive EDI-OCT and OCTA measurements were then analyzed for statistical significance.

2.6. Data analysis

Statistical analysis was carried out by using SPSS software (Version 22, SPSS Inc., Chicago, IL, USA). Descriptive statistical methods (mean, standard deviation) were used in the data evaluation. Categorical variables were analyzed using the Chi-square test. All parameters were analyzed for normality analysis by the Shapiro-Wilk test. Data with normal distribution were analyzed by a paired *t*-test. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Demographic characteristics

Demographic characteristics of the participants are displayed in Table 1. There were 24 (50%) females and 24 (50%) males among the total 48 participants. The average age of caffeinated and decaffeinated coffee consumers was 23.45 ± 0.92 and 22.73 ± 1.13 years, respectively. The two groups did not differ significantly in pre-consumption best-corrected visual acuity ($p = 1.000$), IOP ($p = 0.256$), or axial length ($p = 0.581$).

Table 1
Demographic characteristics of the study participants.

	Caffeinated coffee consumers (n:24) (Mean ± SD)	Decaffeinated coffee consumers (n:24) (Mean ± SD)	*p*-value
Age (year)	23.45 ± 0.92	22.73 ± 1.13	0.407*
Male-to-female ratio	12:12	12:12	1.000+
Best-corrected visual acuity (logMAR)	0.0 ± 0.0	0.0 ± 0.0	1.000*
Intraocular pressure (mmHg)	13.88 ± 2.95	12.60 ± 2.74	0.256*
Axial length (mm)	21.90 ± 2.07	21.83 ± 2.26	0.581*

* = Independent t-test results.
+ = Chi-square test results, logMAR = Logarithm of the Minimum Angle of Resolution, *n* = Number of participants, mmHg = millimeter(s) of mercury, mm = millimeter, SD = Standard deviation.

3.2. Optical coherence tomography and optical coherence tomography angiography analyses

3.2.1. Caffeinated coffee consumers

In comparison to pre-consumption measurement (295.06 ± 5.45 μm), post-consumption SFCT decreased statistically significantly after 30 min (277.08 ± 5.33 μm) and one hour (260.71 ± 58.61 μm) ($p < 0.05$) (Fig. 1); however, post-consumption central macular and retinal nerve fiber layer thicknesses did not ($p > 0.05$). Again, compared to pre-consumption measurement (54.45%), post-consumption parafoveal SCP VD decreased statistically significantly after 30 min (51.80%) and one hour (51.92%) ($p < 0.05$). The same pattern was seen for post-consumption parafoveal DCP VD, which decreased statistically significantly after 30 min (52.45%) and one hour (52.83%) compared to pre-consumption measurements (55.16%) ($p < 0.05$). Changes in foveal and perifoveal SCP and DCP VDs, on the other hand, did not reach statistical significance ($p > 0.05$) (Fig. 2).

The same time intervals were associated with significantly decreased capillary flow areas in the outer retinal (pre-consumption: 8.87 ± 1.91 mm^2 versus 30 min post-consumption: 8.03 ± 1.88 mm^2 versus one hour post-consumption: 8.11 ± 1.93 mm^2), and choriocapillaris layers (pre-consumption: 20.95 ± 0.98 mm^2 versus 30 min post-consumption 19.82 ± 1.20 mm^2 versus one hour post-consumption: 19.62 ± 0.95 mm^2) ($p < 0.05$) (Fig. 3).

However, the effect of caffeinated coffee on EDI-OCT and OCTA parameters six and 24 h later was not statistically significant ($p > 0.05$) (Table 2, Fig. 4). Moreover, post-consumption FAZ parameters (FAZ area, FAZ perimeter, and F-300) did not differ significantly from pre-consumption measurements ($p > 0.05$) (Fig. 5).

3.2.2. Decaffeinated coffee consumers

None of the post-consumption EDI-OCT or OCTA parameters changed statistically significantly when compared to pre-consumption measurements ($p > 0.05$) (Table 2, Fig. 6).

4. Discussion

Caffeine (1,3,7-trimethylxanthine) is a naturally occurring herb alkaloid with a low molecular weight. Its chemical properties, including low hydrophilicity and lipophilicity, allow it to cross all biological membranes and spread throughout the body [21]. This molecule is a commonly used neuro-stimulator present in coffee, tea, cola, soft drinks, chocolate, analgesics, as well as dietary supplements [22]. It is the most widely used, legal, and unregulated psychoactive substance in the world [18,22]. Although approximately 200 ml of caffeinated instant coffee consists of 65–100 mg of caffeine, there is about 5 mg of caffeine in the same volume of instant caffeine-free coffee [23]. Coffee type and brand, method of preparation, amount of water and temperature, and coffee cooling down are all factors that determine the total caffeine content in the drink [1,12,24].

Almost all caffeine consumed orally is absorbed in the gastrointestinal tract [25]. Caffeine plasma concentrations have been shown to peak between 30 and 120 min after consumption [26,27]. It is almost completely metabolized in the liver by the cytochrome P450 enzyme

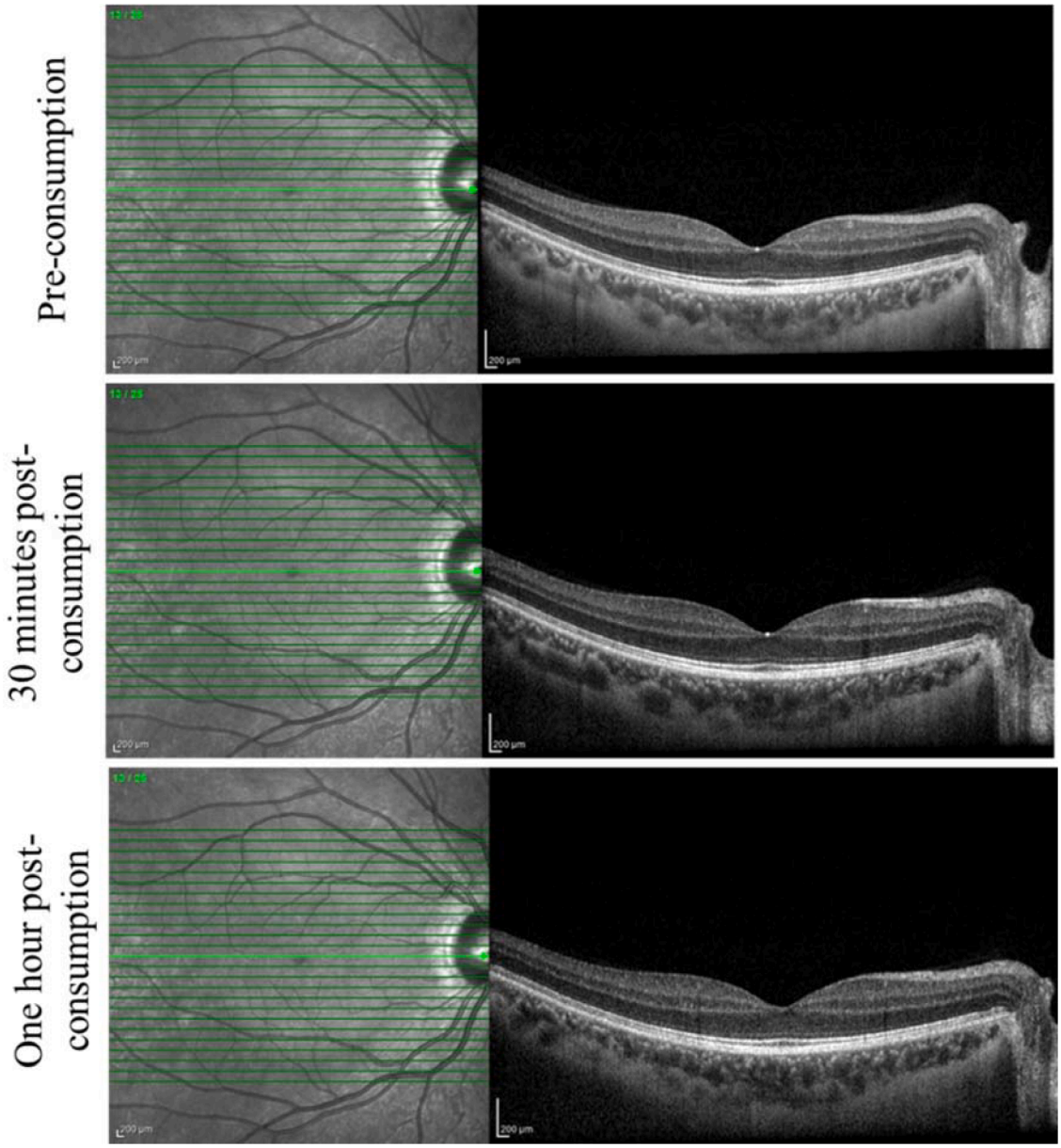

Fig. 1. Caffeinated coffee consumer's right eye EDI-OCT retinal scan through foveal center depicting SFCT changes before consumption, 30 min, and one hour after consumption, which were associated with statistically significant decrease.

system, primarily CYP1A2, with only about 3% excreted unchanged in urine. Among its metabolites are paraxanthine, theobromine, theophylline, 1-methylxanthine, and 1-methyluric acid [28]. Caffeine pharmacokinetics after tea, coffee, cola, capsules, chocolate, or sugar-free cola consumption have all been studied [29,30]. This molecule has the potential to affect blood flow in different sites throughout the human body. Mechanical action of caffeine, which causes many vasoconstrictive events when consumed, involves blocking adenosine A2a receptor, which is one of the key endogenous vasodilators [4,5,31]. This raises peripheral vascular resistance and systemic blood pressure while decreasing heart rate, blood pressure, and flow to the brain and eyes [6,7].

Caffeine has been shown to reduce cerebral blood flow by 15% to 30% [32,33]. Besides, like many other vascular systems, it is likely to have an effect on the ocular microcirculation supplied by the carotid artery and its related branches. Lotfi et al. [34], reported that 200 mg of caffeine decreased retinal blood flow by approximately 13%, and increased diastolic blood pressure by 9% an hour after consumption. Okuno et al. [35], reported that 100 mg caffeine could increase blood vessel resistance and decrease blood flow in the optic nerve head, as well as retinal and choroidal tissues. Ozkan et al. [10], discovered a significant increase in the resistive index of the ophthalmic, central retinal, short posterior, and nasal ciliary arteries an hour after consuming 300 mg of caffeine. Also, Karti et al. [8], reported a significantly decreased macular flow area (superficial, deep, and choriocapillaris) and VD an hour after 200 mg caffeine consumption relative to decaffeinated coffee consumers of 200 mg lactose powder as placebo.

Aside from ocular microcirculation investigations, EDI-OCT has been used to evaluate the SFCT. Vural et al. [36], found that consumption of 100 ml of Turkish coffee induces a significant reduction in the SFCT for at least four hours after consumption. Correspondingly, Zengin et al. [37], discovered that 200 mg of caffeine significantly reduced SFCT after oral consumption, with the effect lasting at least 90 min. They finally hypothesized that this decrease could be due to reduced ocular blood flow induced by caffeine's vasoconstrictive effects. Altinkaynak et al. [38], revealed a 200 mg caffeine-induced SFCT thinning about 30 min

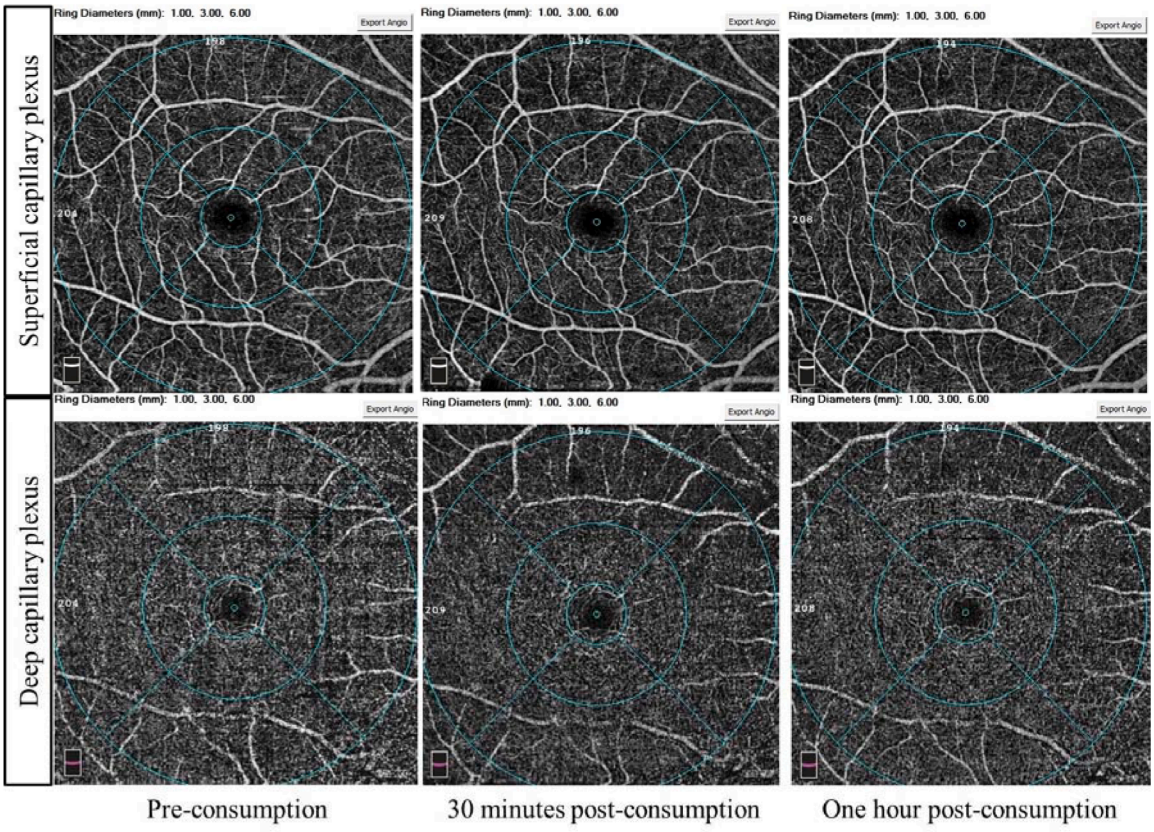

Fig. 2. Caffeinated coffee consumer's right eye OCT angiograms displaying significant decreases in parafoveal superficial and deep capillary plexus vessel densities 30 min and one hour post-consumption. The foveal and periofoveal vessel densities in both superficial and deep capillary plexus did not change significantly during the study period. Scan Quality 9/10.

after oral caffeine ingestion, with a four-hour continuous decline. However, in the same study, the SFCT was reported to normalize after six hours. Moreover, Dervisogullari et al. [39], found a significant reduction in the SFCT after 200 mg of caffeine consumption that prevailed for ≥4 h.

Evidently, all preceding studies concentrated on either the SFCT or ocular microcirculation and found caffeine-induced acute decreases in both parameters. The current study, on the other hand, was designed to investigate changes in retinochoroidal microvascular morphology in relatively young healthy individuals after consuming instant caffeinated versus ground decaffeinated Turkish coffee using both EDI-OCT and OCTA technologies. The caffeine dose was determined on the basis of earlier research on caffeine's effects on ocular microcirculation [10,34, 40]. The parameters were measured before, as well as 30 min, one, six, and 24 h post-consumption, with the durations determined by caffeine's bio-elimination characteristic [41].

In the current study, the absence of statistically significant differences in pre-consumption data between caffeinated and decaffeinated coffee consumers indicated that the study groups included were homogeneous and appropriate for statistical analysis. Caffeinated coffee consumers were found to have relatively transient vasoconstrictive changes occurring immediately after consumption, which was consistent with prior reports. This was also accompanied by a significantly decreased SFCT, as well as the outer retinal and choriocapillaris flow areas. Unlike prior reports, only parafoveal SCP and DCP VDs were found to be significantly decreased. The use of instant coffee (approximately 65–100 mg caffeine) in the current study, just as 200 mg caffeine capsules in the Karti et al. [8], study, could explain these findings. But, Karti et al. [8], only studied the participants one hour after consumption, and did not specify when the caffeine effects ceased. In the current study, on the other hand, the effect of caffeinated coffee was found to begin about 30–60 min after consumption. Apart from the early significant microvascular morphological changes, no significant changes were observed during the sixth and 24th hours, implying that these changes could be ascribable to time-dependent caffeine elimination from the circulatory system. Caffeinated coffee, rather than decaffeinated one, was associated with significant morphological changes in the retinochoroidal microvasculature. The relatively higher caffeine content in caffeinated coffee seems to be associated with these findings. This is due to the fact that no such apparent retinochoroidal microvascular morphological changes were revealed after decaffeinated coffee with low caffeine content of approximately 5 mg was consumed.

Some potential limitations exist in the current study. It was not intended to determine which caffeinated coffee ingredients were accountable for the detected changes. Non-caffeine ingredients of caffeinated coffee could well be involved in the observed retinochoroidal microvascular morphological effects. Despite the fact that there were few healthy volunteers and that only instant coffee was consumed for the study, significant transient caffeine-induced retinochoroidal microvascular morphological changes were revealed. However, more studies involving a relatively larger population and/or individuals of various ages and working groups, as well as the use of different types of coffee, could yield fairly conclusive results. Furthermore, only pre-consumption IOP and axial length were measured; however, caffeine-induced IOP rise has been noted [21]. Given that our study participants were not regular coffee consumers, the effects on people who consume coffee on a daily basis may also differ. Another study is currently underway, involving a fairly diverse age group with varying coffee types and consumption habits, as well as different working groups.

The current study has some strengths as well. Unlike earlier studies on the SFCT and macular microcirculation, we used both the EDI-OCT

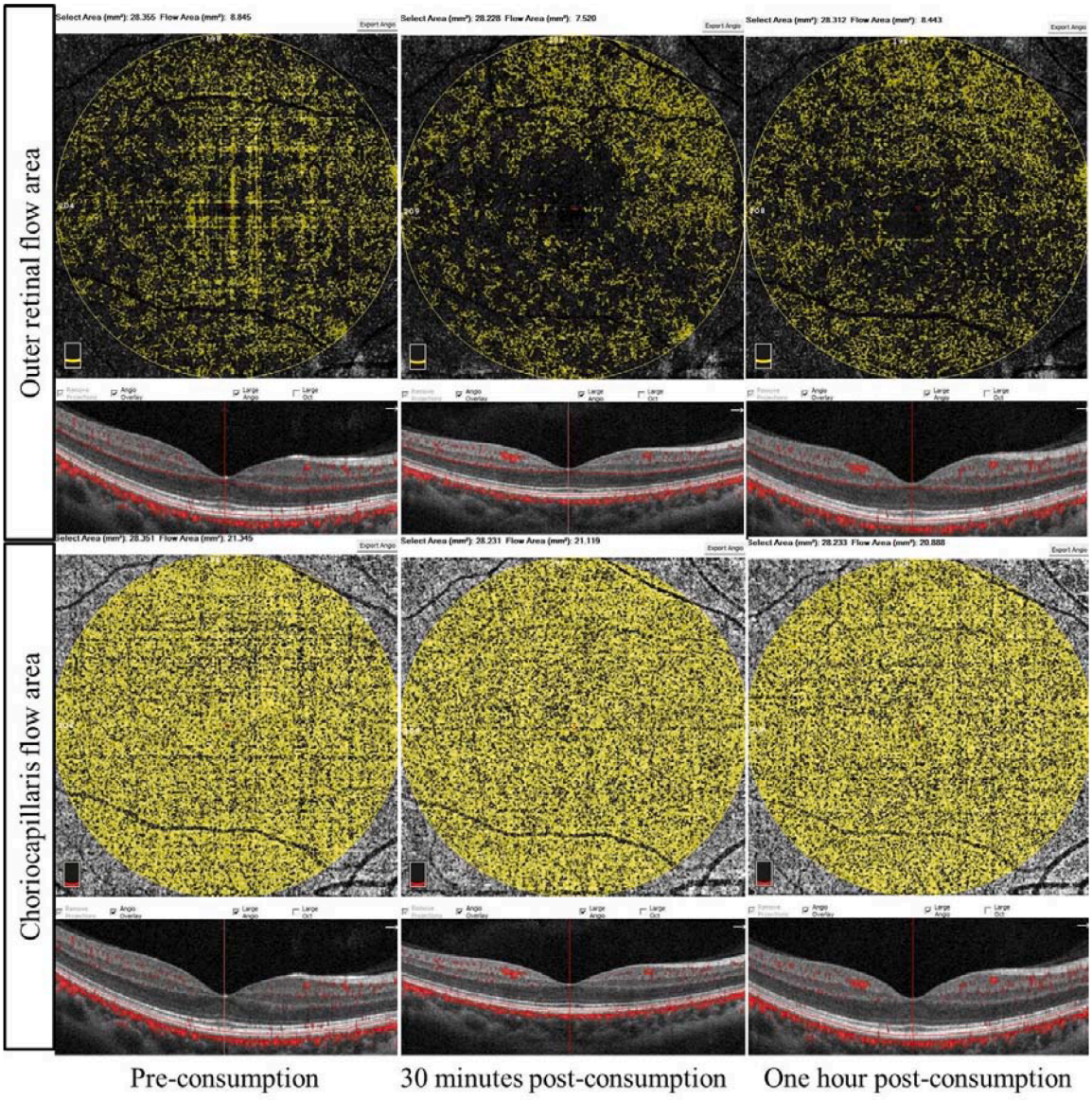

Fig. 3. Caffeinated coffee consumer's right eye OCT angiograms showing significant decreases in capillary low areas in both the outer retinal and choriocapillaris layers 30 min and one hour post-consumption. Below the angiograms are cross-sections demonstrating angio overlays for the retinochoroidal layer. Scan Quality 9/10.

and OCTA technologies to investigate caffeinated versus decaffeinated-induced microvascular morphological changes in relatively younger age- and gender-matched health individuals. This enabled us to investigate caffeine's time–dependent effects on the ultrastructure and microvascular morphology of the retina and choroid simultaneously. Choroidal region is evaluated using the EDI-OCT; however, microcirculation analysis is done indirectly using the SFCT values. The link between the SFCT and choroidal microvascular system is still being questioned [39]. The SFCT is measured manually, which could lead to inter-observer bias. We believe that combining the EDI-OCT and OCTA increases the likelihood of obtaining relatively conclusive results in terms of retinochoroidal microvascular morphological and ultrastructural changes.

5. Conclusions

Caffeinated coffee consumption was found to be associated with significant changes in retinochoroidal microvascular morphology, including parafoveal SCP and DCP VDs, outer retinal and choriocapillaris flow areas, as well as the SFCT. The absence of similar results after decaffeinated coffee consumption could support the role of caffeine in certain vasoconstrictive events. Having said that, these slight and, most likely, transient changes are highly improbable to have clinical implications. The current study's findings suggest that caffeine's effects on capillary flow area and VD should be considered in future investigation of the retinochoroidal microvascular morphology.

Declarations

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Financial interest

All authors certify that they have no affiliations with or involvement

Table 2
Consecutive enhanced depth optical coherence tomography and optical coherence tomography angiography analyses of caffeinated and decaffeinated coffee consumer groups.

Parameters	Groups	Pre-consumption	Post-consumption			
			At 30th min	At 1st hour	At 6th hour	At 24th hour
Foveal avascular zone (mm^2)	1 (n:24)	0.20 ± 0.09	0.21 ± 0.08 (p:0.785)	0.22 ± 0.10 (p:0.662)	0.20 ± 0.09 (p:0.907)	0.21 ± 0.08 (p:0.750)
	2 (n:24)	0.21 ± 008	0.22 ± 0.10 (p:0.612)	0.21 ± 0.09 (p:0.865)	0.22 ± 0.10 (p:0.593)	0.21 ± 0.09 (p:0.882)
Foveal avascular zone perimeter (mm)	1 (n:24)	1.86 ± 0.39	183 ± 0.39 (p:0.427)	1.84 ± 0.41 (p:0.681)	1.81 ± 0.39 (p:0.346)	1.83 ± 0.40 (p:0.418)
	2 (n:24)	1.89 ± 0.40	1.89 ± 0.38 (p:0.783)	1.90 ± 0.38 (p:0.634)	1.89 ± 0.41 (p:0.812)	1.89 ± 0.39 (p:0.753)
FD-300 (%)	1 (n:24)	56.44 ± 3.11	56.06 ± 3.40 (p:0.329)	56.83 ± 2.94 (p:0.307)	56.72 ± 3.69 (p:0.520)	56.50 ± 2.84 (p:0.704)
	2 (n:24)	56.68 ± 2.95	56.41 ± 3.67 (p:0.534)	56.92 ± 3.33 (p:0.586)	56.73 ± 2.84 (p:0.721)	56.53 ± 3.03 (p:0.656)
Outer retinal flow area (mm^2)	1 (n:24)	8.87 ± 1.91	8.03 ± 1.88 (p:0.003)	8.11 ± 1.93 (p:0.010)	8.75 ± 1.88 (p:0.794)	8.62 ± 1.92 (p:0.511)
	2 (n:24)	8.69 ± 1.89	8.52 ± 1.89 (p:0.671)	8.65 ± 1.89 (p:0.913)	8.78 ± 1.87 (p:0.828)	8.49 ± 1.86 (p:0.582)
Choriocapillary flow area (mm^2)	1 (n:24)	20.95 ± 0.98	19.82 ± 1.20 (p:0.008)	19.62 ± 0.95 ($p < 0.001$)	20.59 ± 0.91 (p:0.390)	20.83 ± 0.82 (p:0.747)
	2 (n:24)	20.48 ± 0.78	20.24 ± 0.78 (p:0.586)	20.49 ± 0.76 (p:0.958)	20.31 ± 0.63 (p:0.715)	20.55 ± 0.72 (p:0.795)
Sub-foveal choroidal thickness (μm)	1 (n:24)	295.06 ± 58.42	277.08 ± 56.33 (p:0.029)	260.71 ± 58.61 ($p < 0.001$)	292.15 ± 60.58 (p:0.818)	299.26 ± 59.07 (p:0.749)
	2 (n:24)	288.25 ± 59.14	284.72 ± 57.21 (p:0.764)	290.17 ± 60.52 (p:0.820)	287.17 ± 55.12 (p:0.899)	288.09 ± 58.91 (p:0.935)
Central macular thickness (μm)	1 (n:24)	224.75 ± 18.03	225.30 ± 18.85 (p:0.629)	222.84 ± 20.62 (p:0.455)	224.96 ± 19.45 (p:0.816)	225.97 ± 17.35 (p:0.517)
	2 (n:24)	227.14 ± 17.23	224.49 ± 24.02 (p:0.409)	226.08 ± 16.05 (p:0.588)	223.79 ± 18.26 (p:0.267)	224.30 ± 16.46 (p:0.386)
Retinal nerve fiber layer thickness (μm)	1 (n:24)	99.49 ± 9.06	98.22 ± 9.54 (p:0.330)	99.15 ± 10.11 (p:0.861)	99.92 ± 11.93 (p:0.805)	98.73 ± 9.73 (p:0.540)
	2 (n:24)	99.07 ± 11.17	99.61 ± 9.66 (p:0.758)	98.57 ± 11.97 (p:0.694)	99.61 ± 10.01 (p:0.671)	99.50 ± 9.91 (p:0.792)

Group 1 = Caffeinated coffee consumers, Group 2 = Decaffeinated coffee consumers, FD-300 = Foveal vessel density in a 300 μm wide region around foveal avascular zone, *n* = Number of participants, mm = millimeter, mm^2 = Millimeter square, μm = Micrometer,% = Percentage. Results of the comparison with the pre-consumption *t*-test are indicated in parentheses. $p < 0.05$ in bold was considered statistically significant.

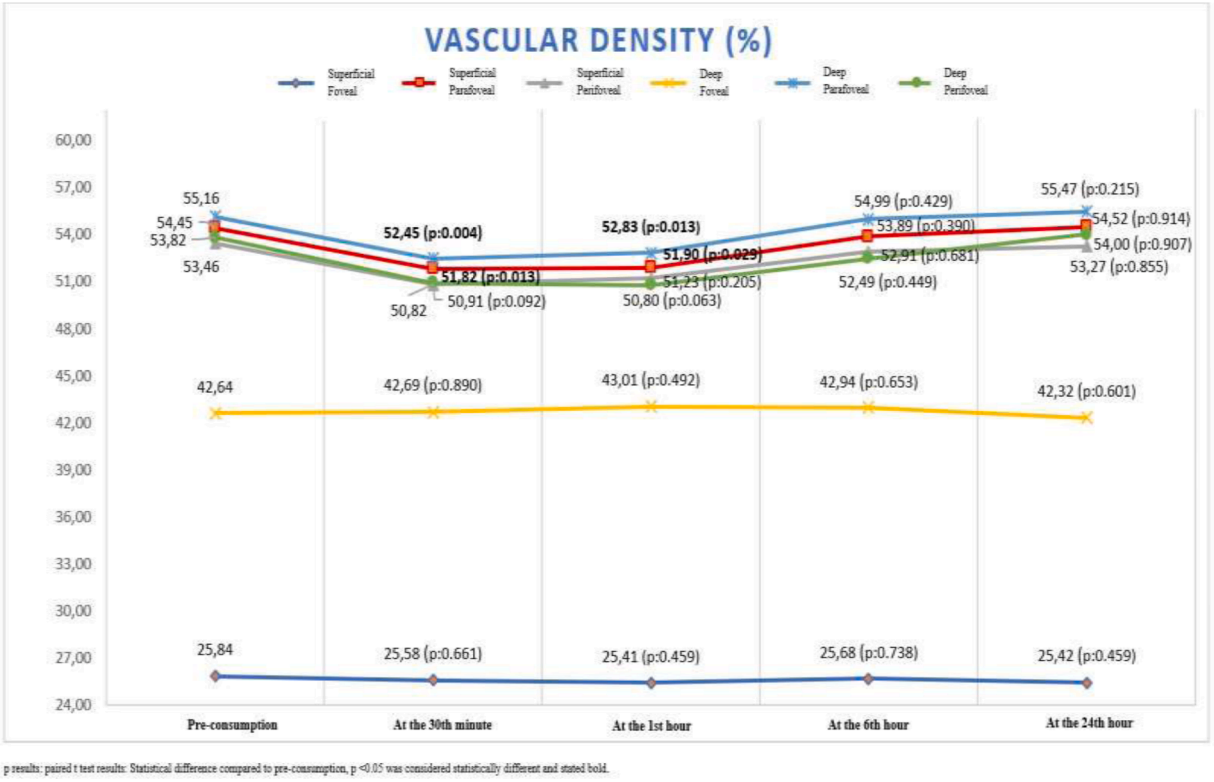

Fig. 4. Graphical display of consecutively measured macular vessel densities in caffeinated coffee consumers.

in any organization or entity with any financial interest or non-financial interest in the subject matter or materials mentioned in this article.

Ethics approval

The study procedure abided by the ethical standards of the Helsinki Declaration and obtained full approval from the Institutional Review Boards of the Afyonkarahisar Health Sciences University Ethics Committee. Prior to the study, all participants issued informed written consent.

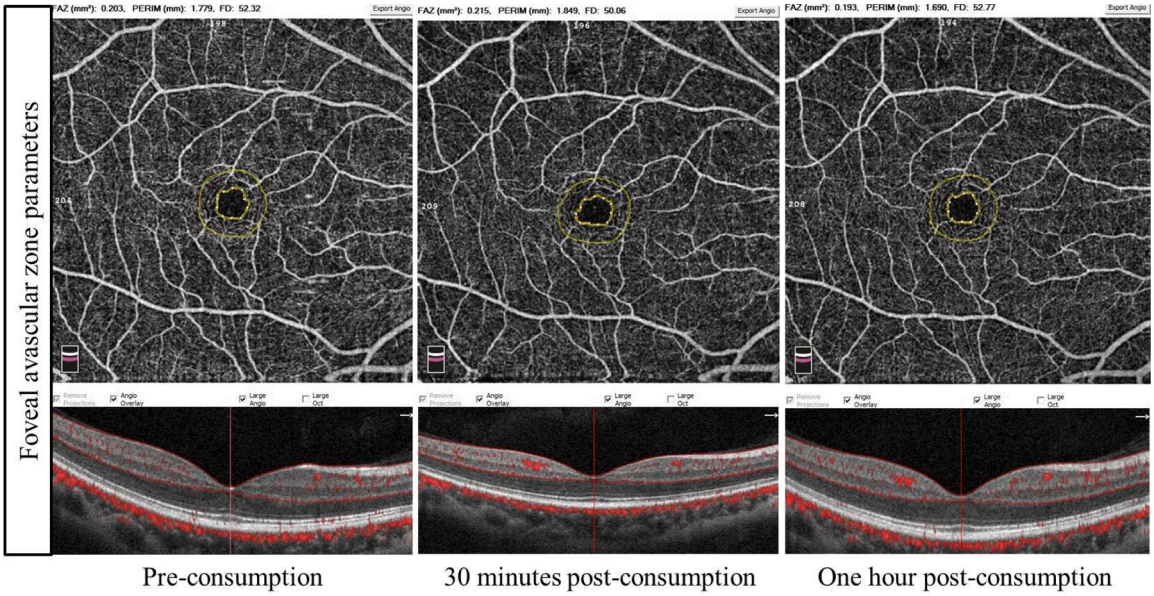

Fig. 5. Caffeinated coffee consumer's right eye OCT angiograms. Caffeine had no significant effect on any of the foveal avascular zone parameters, including foveal avascular zone area, foveal avascular zone perimeter, or foveal vessel density in a 300-μm wide region around foveal avascular zone (FD-300). The angiograms are accompanied by cross-sections of the retinochoroidal layer with angio overlays. Scan Quality 9/10.

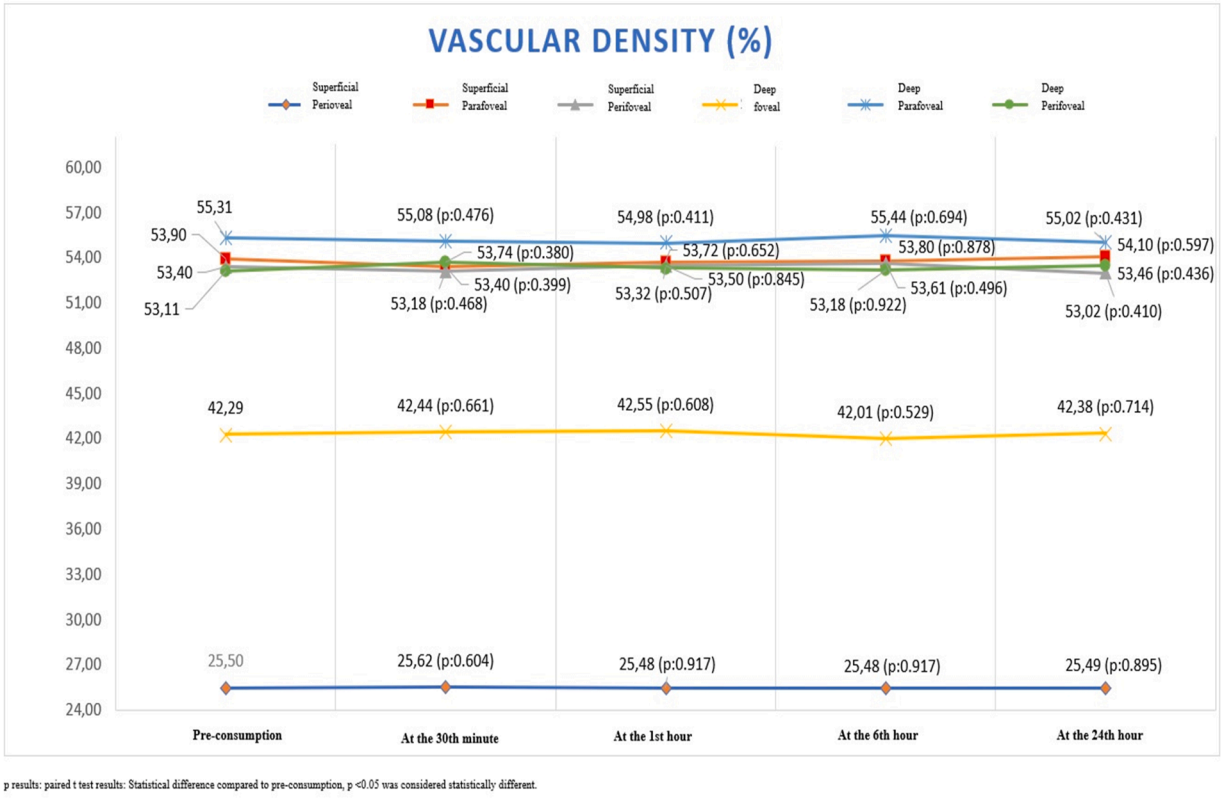

Fig. 6. Graphical display of consecutively measured macular vessel densities in decaffeinated coffee consumers.

Consent to participate and consent for publication

My colleagues and I conducted the research and co-authored the manuscript. We have all approved the manuscript for submission and publication in your journal, and I am the corresponding author.

Availability of data and material

The manuscript contains all data. The datasets used and/or analyzed during the current study, however, are available upon reasonable request from the corresponding author.

CRediT authorship contribution statement

Mustafa Dogan: Project administration, Conceptualization, Methodology, Software. **Muberra Akdogan:** Methodology, Data curation, Writing – review & editing. **Mehmet Cem Sabaner:** Visualization, Investigation, Methodology. **Hamidu Hamisi Gobeka:** Formal analysis, Visualization, Investigation, Writing – original draft.

Declaration of Competing Interest

The author(s) declare(s) no conflict of interest.

References

[1] R.R. McCusker, B.A. Goldberger, E.J. Cone, Caffeine content of specialty coffees, J. Anal. Toxicol. 27 (2003) 520–522.
[2] J.W. Daly, B.B. Fredholm, Caffeine: an untypical drug of dependence, Drug Alcohol Depend. 51 (1998) 199–206.
[3] R. Poole, O.J. Kennedy, P. Roderick, J.A. Fallowfield, P.C. Hayes, J. Parkes, Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes, BMJ 359 (2017) j5024.
[4] K. Nieber, The impact of coffee on health, Planta Med. 83 (2017) 1256–1263.
[5] E.A. Newman, Functional hyperemia and mechanisms of neurovascular coupling in the retinal vasculature, J. Cereb. Blood Flow Metab. 33 (2013) 1685–1695.
[6] D. Turnbull, J.V. Rodricks, G.F. Mariano, F. Chowdhury, Caffeine and cardiovascular health, Regul. Toxicol. Pharmacol. 89 (2017) 165–185.
[7] E. Casiglia, S. Bongiovì, C.D. Paleari, S. Petucco, M. Boni, G. Colangeli, M. Penzo, A.C. Pessina, Haemodynamic effects of coffee and caffeine in normal volunteers: a placebo-controlled clinical study, J. Intern. Med. 229 (1991) 501–504.
[8] O. Karti, M.O. Zengin, S.G. Kerci, Z. Ayhan, T. Kusbeci, Acute effect of caffeine on macular microcirculation in healthy subjects: an optical coherence tomography angiography study, Retina 39 (2019) 964–971.
[9] N. Terai, E. Spoerl, L.E. Pillunat, R. Stodtmeister, The effect of caffeine on retinal vessel diameter in young healthy subjects, Acta Ophthalmol. 90 (2012) e524–e528.
[10] B. Ozkan, N. Yüksel, Y. Anik, O. Altintas, A. Demirci, Y. Cağlar, The effect of caffeine on retrobulbar hemodynamics, Curr. Eye Res. 33 (2008) 804–809.
[11] I. Guessous, C.B. Eap, M. Bochud, Blood pressure in relation to coffee and caffeine consumption, Curr. Hypertens. Rep. 16 (2014) 468.
[12] R.R. McCusker, B. Fuehrlein, B.A. Goldberger, M.S. Gold, E.J. Cone, Caffeine content of decaffeinated coffee, J. Anal. Toxicol. 30 (2006) 611–613.
[13] J. Kur, E.A. Newman, T. Chan-Ling, Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease, Prog. Retin. Eye Res. 31 (2012) 377–406.
[14] R.L. Engerman, Development of the macular circulation, Invest. Ophthalmol. 15 (1976) 835–840.
[15] W. Choi, K.J. Mohler, B. Potsaid, C.D. Lu, J.J. Liu, V. Jayaraman, A.E. Cable, J. S. Duker, R. Huber, J.G. Fujimoto, Choriocapillaris and choroidal microvasculature imaging with ultrahigh speed OCT angiography, PLoS ONE 8 (2013) e81499.
[16] R.F. Spaide, H. Koizumi, M.C. Pozzoni, Enhanced depth imaging spectral-domain optical coherence tomography, Am. J. Ophthalmol. 146 (2008) 496–500.
[17] Coffee Statistics Report 2011. http://www.coffee-statistics.com/coffee_statistics_ebook.html. accessed 25 May 2011.
[18] D.C. Mitchell, C.A. Knight, J. Hockenberry, R. Teplansky, T.J. Hartman, Beverage caffeine intakes in the U.S, Food Chem. Toxicol. 63 (2014) 136–142.
[19] J. Sahni, P. Stanga, D. Wong, S. Harding, Optical coherence tomography in photodynamic therapy for subfoveal choroidal neovascularisation secondary to age related macular degeneration: a cross sectional study, Br. J. Ophthalmol. 89 (2005) 316–320.
[20] Y. Jia, O. Tan, J. Tokayer, B. Potsaid, Y. Wang, J.J. Liu, M.F. Kraus, H. Subhash, J. G. Fujimoto, J. Hornegger, D. Huang, Split-spectrum amplitude-decorrelation angiography with optical coherence tomography, Opt. Express 20 (2012) 4710–4725.
[21] J.J. Yoon, H.V. Danesh-Meyer, Caffeine and the eye, Surv. Ophthalmol. 64 (3) (2019) 334–344.
[22] G. Renda, R.C De Caterina, R. De Caterina, J.A. Martinez, M. Kohlmeier, Principles of Nutrigenetics and Nutrigenomics: Fundamentals of Individualized Nutrition, Academic Press Elsevier Inc, 2020, pp. 335–340.
[23] H. Daries, Nutrition for sport and exercise [Internet]. Nutrition for Sport and Exercise The 3rd Edition, John Wiley & Sons, Ltd, West Sussex, UK, 2013, p. 383.
[24] I. Hečimović, A. Belščak-Cvitanović, D. Horžić, D. Komes, Comparative study of polyphenols and caffeine in different coffee varieties affected by the degree of roasting, Food Chem. 129 (2011) 991–1000.
[25] M. Bonati, R. Latini, F. Galletti, J.F. Young, G. Tognoni, S. Garattini, Caffeine disposition after oral doses, Clin. Pharmacol. Ther. 32 (1982) 98–106.
[26] H.G. Mandel, Update on caffeine consumption, disposition and action, Food Chem. Toxicol. 40 (2002) 1231–1234.
[27] J.A. Carrillo, J. Benitez, Clinically significant pharmacokinetic interactions between dietary caffeine and medications, Clin. Pharmacokinet. 39 (2000) 127–153.
[28] M. Kot, W.A. Daniel, Caffeine as a marker substrate for testing cytochrome P450 activity in human and rat, Pharmacol. Rep. 60 (2008) 789–797.
[29] A. Liguori, J. Hughes, J. Grass, Absorption and subjective effects of caffeine from coffee, cola, and capsules, Pharmacol. Biochem. Behav. 58 (1997) 721–726.
[30] G. Mumford, N. Benowitz, S. Evans, Absorption rate of methylxanthines following capsules, cola, and chocolate, Eur. J. Clin. Pharmacol. 51 (1996) 319–325.
[31] T.M. McLellan, J.A. Caldwell, H.R. Lieberman, A review of caffeine's effects on cognitive, physical and occupational performance, Neurosci. Biobehav. Rev. 71 (2016) 294–312.
[32] R.J. Mathew, W.H. Wilson, Caffeine-induced changes in cerebral circulation, Stroke 16 (1985) 814–817.
[33] M.A. Addicott, L.L. Yang, A.M. Peiffer, L.R. Burnett, J.H. Burdette, M.Y. Chen, S. Hayasaka, R.A. Kraft, J.A. Maldjian, P.J. Laurienti, The effect of daily caffeine use on cerebral blood flow: how much caffeine can we tolerate? Hum. Brain Mapp. 30 (2009) 3102–3114.
[34] K. Lotfi, J.E. Grunwald, The effect of caffeine on the human macular circulation, Invest. Ophthalmol. Vis. Sci. 32 (1991) 3028–3032.
[35] T. Okuno, T. Sugiyama, M. Tominaga, S. Kojima, T. Ikeda, Effects of caffeine on microcirculation of the human ocular fundus, Jpn. J. Ophthalmol. 46 (2002) 170–176.
[36] A.D. Vural, N. Kara, N. Sayin, D. Pirhan, H.B. Ersan, Choroidal thickness changes after a single administration of coffee in healthy subjects, Retina 34 (2014) 1223–1228.
[37] M.O. Zengin, E. Cinar, E. Karahan, I. Tuncer, C. Kucukerdonmez, The effect of caffeine on choroidal thickness in young healthy subjects, Cutan. Ocul. Toxicol. 34 (2015) 112–116.
[38] H. Altinkaynak, E. Ceylan, B. Kartal, S. Keleş, M. Ekinci, O.O. Olcaysu, Measurement of choroidal thickness following caffeine intake in healthy subjects, Curr. Eye Res. 41 (2016) 708–714.
[39] M.S. Dervişoğulları, Y. Totan, A. Yüce, A.E. Kulak, Acute effects of caffeine on choroidal thickness and ocular pulse amplitude, Cutan. Ocul. Toxicol. 35 (2016) 281–286.
[40] M.O. Zengin, E. Cinar, C. Kucukerdonmez, The effect of nicotine on choroidal thickness, Br. J. Ophthalmol. 98 (2014) 233–237.
[41] K. Gilliland, D. Andress, Ad lib caffeine consumption, symptoms of caffeinism, and academic performance, Am. J. Psychol. 138 (1981) 512–514.