Research Article

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Impacts of *Camellia sinensis* fermentation end-product (black tea) on retinal microvasculature: an updated OCTA analysis

Mustafa Doğan,[a*] Müberra Akdoğan,[a] Anar Alizada,[b] Özgür Eroğul,[a] Mehmet Cem Sabaner,[a] Hamidu Hamisi Gobeka,[c] Furkan Fatih Gülyeşil[a] and Mehmet Akif Seylan[d]

Abstract

BACKGROUND: Tea, second only to water, is one of the most regularly consumed drinks in the world. Its potentially beneficial effects on general health may be enormously important. Optical coherence tomography angiography (OCTA) now allows clinicians to examine the acute retinal morphological changes caused by black tea consumption. The purpose of this study was to investigate the acute impacts of a *Camellia sinensis* fermentation end-product (black tea) on retinal microvasculature in healthy individuals using OCTA.

RESULTS: In this study, 60 healthy people were divided into two groups: group 1 ($n = 30$) received black tea (2 mg/250 mL of water) and group 2 ($n = 30$) received only 250 mL of water. Following consumption, AngioVue Analytics software automatically analyzed the foveal, parafoveal, perifoveal macular superficial and deep vascular plexus densities, foveal avascular zone (FAZ) area, FAZ perimeter and foveal vessel density in a 300 μm wide region around the FAZ (FD-300). Male-to-female ratios were 19:11 and 15:15 in groups 1 and 2, respectively ($P = 0.217$). Mean age was 33.27 ± 7.92 years in group 1 and 31.00 ± 7.30 years in group 2 ($P = 0.254$). Changes in foveal, perifoveal and parafoveal macular vessel density between groups 1 and 2 were not statistically significant. In addition, no significant differences regarding FAZ, FAZ perimeter and FD-300 were observed.

CONCLUSION: There were no acute effects of black tea on macular microcirculation in healthy individuals. The authors, however, believe that this study could serve as a model for future research on the relationship between regular tea consumption and general ocular physiology.

Keywords: black tea consumption; *Camellia sinensis*; FAZ; OCTA; retinal microcirculation; vessel density

INTRODUCTION

Tea is the world's second most popular drink, after water. Its potentially beneficial impacts on general well-being could be profound. Around 6 g of tea is consumed every day by a 60 kg person. Black tea is produced from green tea through fermentation of *Camellia sinensis* leaves and accounts for approximately 80% of global tea output. A group of polyphenols called catechins are major ingredients found in teas.[1] Catechins in black tea are transformed into complex condensing products such as theaflavins and thearubigins, which give the brew its characteristic rich color. Aside from catechins and theaflavins, black tea contains a variety of other compounds such as flavonoids and phenolic acids that may have health-promoting properties. In addition, black tea has essential antioxidant ability,[2,3] as well as low amounts of caffeine.[4]

Optical coherence tomography angiography (OCTA; Optovue, Inc., Fremont, CA, USA) is a cutting-edge non-invasive imaging technique that has recently been introduced in ophthalmology clinics. It enables ophthalmologists to visualize both retinal and choroidal capillary systems, as well as foveal avascular zone, without the use of any exogenous dye. Furthermore, this imaging technique can detect different retinal ischemic diseases on clinically undetectable fundus lesions.[5,6] OCTA can also generate three-dimensional and en face imaging of the retinal capillary networks because of its split spectrum amplitude-decorrelation angiography property. This property reduces the signal-to-noise ratio of flow detection, allowing for better visualization of retinal

* *Correspondence to: M Doğan, Department of Ophthalmology, Afyonkarahisar Health Sciences University, Zafer Sağlık Külliyesi A Blok, Dörtyol Mah. 2078 Sokak, No. 3, Pk. 03030, Afyonkarahisar, Turkey. E-mail: mustafadogan@yahoo.com*

a *Department of Ophthalmology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey*

b *Ermeneke State Hospital, Ophthalmology Clinic, Karaman, Turkey*

c *Department of Ophthalmology, Agri Ibrahim Cecen University Faculty of Medicine, Ağrı, Turkey*

d *Istanbul Kanuni Sultan Suleyman Educational and Research Hospital Ophthalmology Clinic, Istanbul, Turkey*

vasculature via motion contrast. OCTA is now commonly used for the diagnosis and assessment of vascular-related retinal and/or choroidal diseases such as diabetic retinopathy, choroidal neovascularization, age-related macular degeneration, retinal artery and vein occlusions, and glaucoma.[6–8]

The purpose of this study was to investigate the acute impacts of a *Camellia sinensis* fermentation end-product (black tea) on retinal morphology, particularly macular microcirculation, in healthy individuals using OCTA (Figs 1 and 2).

MATERIALS AND METHODS

Study participants and ophthalmological examination

This prospective, single-centered, placebo-controlled study enrolled 60 eyes of 60 healthy individuals. Participants were divided into two groups: one for the study (group 1; $n = 30$) that received black tea (2 mg/250 mL of water) and another for the placebo (group 2; $n = 30$) that received only 250 mL of water. 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 (Code of acceptance: 2019/335). Formal informed consent was obtained prior to the study.

A comprehensive ophthalmological examination was performed, which included best-corrected visual acuity measurements, Goldmann applanation tonometry, and anterior and posterior segment slit-lamp biomicroscopy. All tests were conducted under standard conditions by the same clinician. Participants were healthy, with no ocular or systemic disorders, did not wear contact lenses, were not pregnant and were not breast-feeding. The study did not involve individuals who recently had eye lubricants, eye surgery or treatment attributable to any local and/or systemic diseases.

OCTA scanning

A tea bag (about 2 mg) was placed in 250 mL of hot water (approximately 95 °C) and left to brew for 3 min before being given to group 1 participants. Meanwhile, group 2 participants received only 250 mL of natural spring water. Either drink was consumed within approximately 5 min. OCTA was performed under Angio Retina mode (6 × 6 mm) before and 1 h after consumption of the respective drinks. To avoid diurnal fluctuation, OCTA was performed concurrently during the day (between 9:00 a.m. and 11:00 a.m.) after at least 8 h of hunger duration.

Eye movement artefacts were minimized by an eye-tracking mode and eliminated by a motion correction technology. All scans were checked to ensure appropriate segmentation and image quality (quality index ≥ 7). Poor-quality scans were discarded from the study. Vessel densities in the superficial retinal layer (superficial capillary plexus) and deep retinal layer (deep capillary plexus) were automatically quantified by AngioVue Analytics, RTVue-XR version 2017.1.0.155 software. OCTA was used to obtain retinal morphological parameters such as foveal, parafoveal and perifoveal macular superficial and deep vascular plexus densities. In the meantime, the foveal avascular zone, foveal avascular zone perimeter and foveal vascular density were also obtained from the software's foveal avascular zone mode in 300 μm wide regions around the foveal avascular zone.

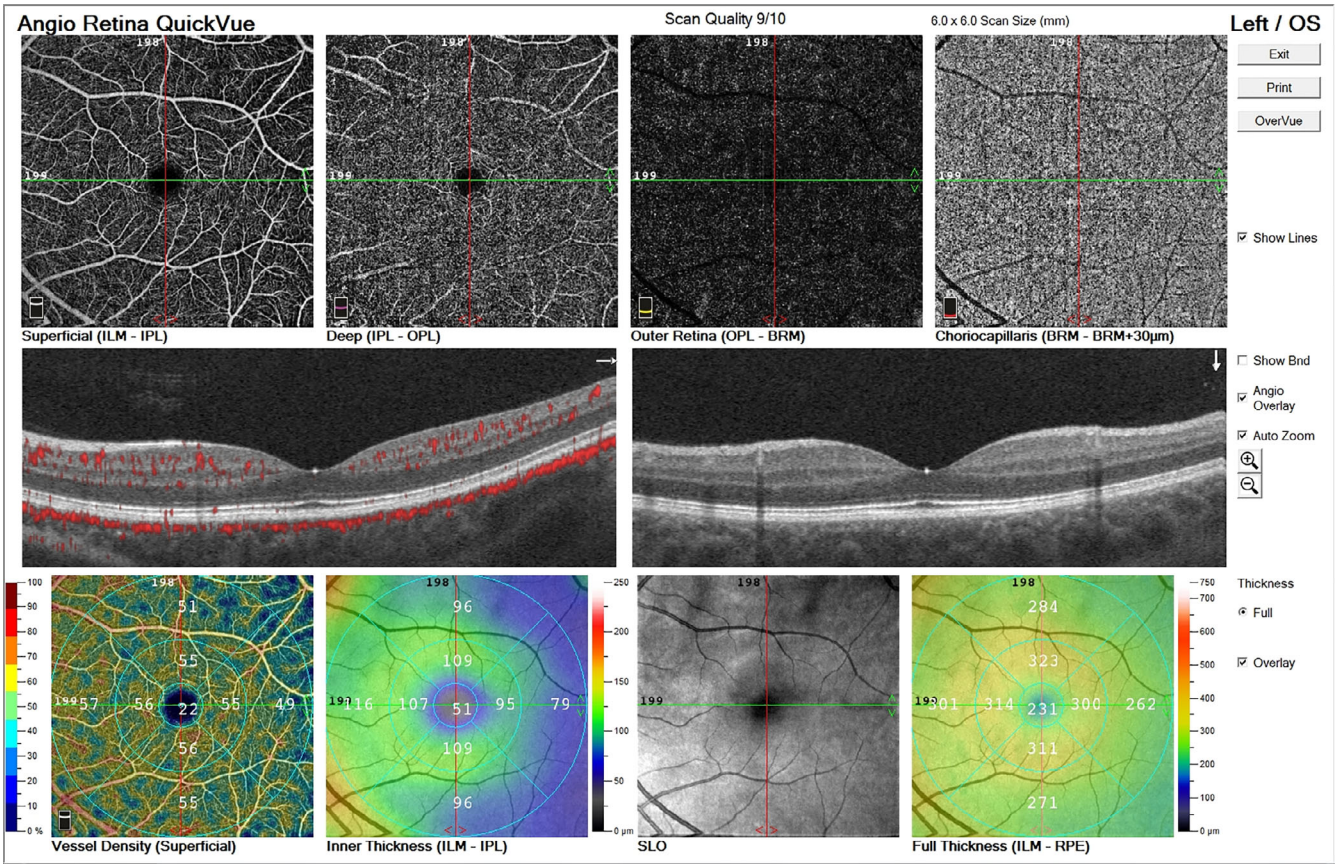

Figure 1. Visualization of superficial and deep vascular plexus with optical coherence tomography angiography.

Figure 2. Visualization of foveal avascular zone and related parameters with optical coherence tomography angiography.

Table 1. Demographic characteristics of the respective groups

	Tea consumption group ($n = 30$)	Water consumption group ($n = 30$)	*P*-value
Age (year)	33.27 ± 7.92	31.00 ± 7.30	0.254[a]
Male:female ratio	19:11	15:15	0.217[b]
BCVA (log MAR)	0.0 ± 0.0	0.0 ± 0.0	1.000[a]
Axial length (mm)	21.18 ± 1.92	21.80 ± 2.75	0.357[a]

[a] Independent *t*-test results.
[b] Chi-square test results.
BCVA, best-corrected visual acuity; *n*, number of participants; $P < 0.05$ was considered statistically significant.

Statistics

Statistical analysis was performed using SPSS software (Version 18, SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft Corp., Redmond, WA, USA). The data was evaluated using descriptive statistical methods (mean, standard deviation). The categorical variables were analyzed using the chi-square test. The Shapiro–Wilk test for normality was used to analyze the distribution of all parameters. The Wilcoxon test was used to determine the significance of the difference in abnormal distribution parameters between two consecutive measurements. The analysis was performed at the 95% confidence interval, and $P < 0.05$ indicated a statistically significant difference.

RESULTS

Male-to-female ratios in group 1 were 19:11, and 15:15 in group 2. Group 1 had an average age of 33.27 ± 7.92 years, while group 2 had an average age of 31.00 ± 7.30 years. Table 1 shows the demographic characteristics of the respective groups.

Changes in retinal morphological parameters, such as foveal, perifoveal and parafoveal macular vascular plexus densities, were statistically non-significant between the two groups after respective drink consumption (Table 2). Furthermore, no significant differences in parameters such as foveal avascular zone, foveal avascular zone perimeter and foveal vascular density 300 µm wide regions around the foveal avascular zone were found between the two groups (Table 3).

DISCUSSION

In this study, OCTA was used to investigate acute changes in retinal morphology, particularly at the level of macular microcirculation, after the consumption of black tea in healthy individuals. OCTA is a modern technology with enormous clinical potential. It has advantages such as being non-invasive, obtaining

Table 2. Changes in retinal vessel density parameters before and after consumption of the respective drinks

Parameter (%)	Group	*n*	Before consumption [median (min–max)]	After consumption [median (min–max)]	*P*-value[a]
Whole superficial	Group 1	30	50.60 (44.80–58.00)	50.95 (44.70–56.10)	0.227
	Group 2	30	51.90 (49.80–54.60)	51.85 (48.50–54.60)	0.424
Foveal superficial	Group 1	30	23.65 (14.00–33.20)	21.05 (11.60–32.90)	0.070
	Group 2	30	23.60 (10.90–32.40)	23.55 (11.80–30.90)	0.461
Parafoveal superficial	Group 1	30	54.10 (47.50–58.70)	54.45 (41.70–58.60)	0.707
	Group 2	30	53.60 (51.90–56.60)	53.75 (50.10–55.40)	0.576
Perifoveal superficial	Group 1	30	51.30 (44.60–59.40)	51.95 (45.70–56.80)	0.311
	Group 2	30	51.75 (50.80–55.60)	51.85 (50.80–56.80)	0.945
Whole deep	Group 1	30	55.60 (42.00–62.90)	57.00 (44.70–64.30)	0.125
	Group 2	30	59.74 (44.80–65.40)	60.05(49.20–65.70)	0.100
Foveal deep	Group 1	30	40.45 (31.90–49.70)	40.20 (16.20–52.00)	0.797
	Group 2	30	32.70 (28.60–48.60)	30.40 (28.70–43.90)	0.789
Parafoveal deep	Group 1	30	57.85 (42.50–62.00)	59.10 (45.10–69.20)	0.168
	Group 2	30	62.35 (47.80–66.10)	62.65 (53.20–66.10)	0.156
Perifoveal deep	Group 1	30	59.85 (44.50–64.50)	59.80 (37.70–66.00)	0.062
	Group 2	30	61.65 (44.90–67.40)	62.30 (45.00–67.40)	0.078

[a] Wilcoxon test results: statistical differences between before and after consumption; $P < 0.05$ was considered statistically significant.
n, number of participants; Group 1, tea consumption; Group 2, water consumption.

Table 3. Changes in foveal avascular zone parameters before and after the respective drink consumption

Parameter	Group	*n*	Before consumption [median (min–max)]	After consumption [median (min–max)]	*P*-value[a]
FAZ[b] area (mm^2)	Group 1	30	0.251 (0.127–0.440)	0.261 (0.120–0.682)	0.194
	Group 2	30	0.240 (0.128–0.392)	0.241 (0.128–0.395)	0.367
PERIM[c](mm)	Group 1	30	1.94 (1.37–2.53)	2.03 (1.33–3.42)	0.096
	Group 2	30	1.71 (1.39–2.39)	1.71 (1.39–2.41)	0.094
FD-300 area[d] (%)	Group 1	30	55.70 (49.41–65.31)	55.64 (47.74–64.00)	0.484
	Group 2	30	53.10 (49.41–62.11)	52.63 (49.41–62.11)	0.603

[a] Wilcoxon test results: statistical differences between before and after consumption; $P < 0.05$ was considered statistically significant.
Group 1, tea consumption; Group 2, water consumption; FAZ, foveal avascular zone; PERIM, foveal avascular zone perimeter (mm); FD-300 area, vessel density 300 µm around the FAZ; *n*, number of participants.

volumetric scans that can be segmented to precise depths, using contrasting motion rather than intravenous dye, providing accurate size and position details, visualizing the retinal and choroidal vasculatures, and monitoring structural and blood flow information simultaneously within seconds.[6,7]

The majority of ocular microcirculation studies using OCTA in the literature have been performed regardless of tea, or specifically black tea conditions. There is insufficient knowledge on normative databases and their applicability in retinal pathologies, even with the newly available OCTA. Matsunaga *et al.*[9] stated that in normal subjects OCTA generates high-resolution, non-invasive angiograms qualitatively comparable to traditional fluorescein angiography. Moreover, many standard population studies have shown variations in foveal thickness, foveal avascular zone shape and region.[10,11] The human retinal capillary network consists of distinct layers of vessels and capillaries, including the deep and superficial vascular plexus.[12] Samara *et al.*[13] used OCTA to examine the superficial and deep capillary plexus foveal avascular zone region in 70 healthy eyes and found age and gender correlations. They reported a variable foveal avascular zone area within the standard population. Savastano *et al.*[14] identified different vascular networks in the inner retina, i.e. superficial and deep networks, using OCTA. Another investigation conducted by Fujiwara *et al.*[15] revealed a negative impact of the central retinal thickness and retinal vascular density on the superficial foveal avascular zone area in 144 normal participants using OCTA.

On the other hand, in this study OCTA was used to determine the acute impacts of a *Camellia sinensis* end-product (black tea) on retinal morphology, particularly at the macular level in healthy individuals. Although differences between the two groups were not statistically significant, there were changes in OCTA parameters such as foveal, perifoveal and parafoveal macular vascular densities, foveal avascular zone, foveal avascular zone perimeter and foveal vascular density 300 µm wide regions around the foveal avascular zone after black tea consumption. There appear to be a plethora of studies that have studied either the OCTA characteristic features in healthy individuals or the effects of green tea extracts on general ocular physiology. However, because there have been no prior studies on the acute impacts of black tea consumption, primarily on retinal morphology using OCTA, this study may serve as a benchmark for this very intriguing topic.

Caffeine in black tea is a powerful methylxanthine that stimulates nervous activity and increases vascular tone.[4] The underlying mechanisms of caffeine's behavior are not well understood. However, its pharmacological effects are thought to be primarily due to its well-established role as an adenosine receptor antagonist.[16] Several studies have reported the effects of caffeine in particular, rather than black tea in general, on blood flow in different parts of the human body.[16,17] Vidyasagar *et al*.[18] investigated the effects of tea components on cerebral blood flow in 20 healthy people and discovered high, locally specific reductions in cerebral blood flow after caffeine administration. There was, however, no evidence that the flavonoids had any effect on cerebral blood flow, implying that only caffeine could cause acute cerebral blood flow changes. Zhang *et al*.[19] stated that caffeine generally causes a pattern of delayed vascular response in all three macular capillary plexuses in response to ambient light. Finally, they hypothesized that these delayed vascular responses could pose a risk of capillary ischemia. In another randomized placebo-controlled OCTA study reported by Karti *et al*.,[20] in which 52 healthy subjects were randomly assigned to a control group with a 200 mg lactose powder placebo capsule and a study group with a 200 mg caffeine capsule, there were no statistically significant differences in baseline macular flow area, vascular density or foveal avascular zone area parameters.

This study, on the other hand, found no significant differences in retinal morphology in terms of perifoveal and parafoveal macular superficial and deep vascular density parameters between black tea and placebo conditions. The non-significant results of this study could be attributed to a relatively lower caffeine content of around 2–4% in black tea, regardless of other components such as flavonoids. Furthermore, the impacts of specific black tea components were not assessed separately in this study. Instead, the goal was to gain a broad understanding of the acute impacts of black tea on retinal morphology.

Tea and its flavonoid constituents have a positive effect on endothelial function, which is a strong predictor of cardiovascular disease risk.[21] Brachial artery flow-induced dilation is an indicator of endothelial function, and several studies have consistently shown that tea and other flavonoid-rich foods have a positive effect on it.[22,23] Tea and its flavonoids improve endothelial nitric oxide synthase activity by enzyme phosphorylation.[24] According to Saito *et al*.,[25] theaflavins can alter hemodynamics in both rats and healthy people. As a result, they proposed that the sympathetic nervous system was involved in theaflavin-induced hemodynamic alterations.

Long-term exposure to intermediate reactive oxygen can harm retinal tissue cells, particularly photoreceptor cells, retinal pigment epithelium and choriocapillaries, resulting in retinal ganglion cell death.[26] Black tea contains catechins in simple, oxidized and polymerized forms, all of which are antioxidants. Furthermore, black tea produces the same amount of polyphenol antioxidants as green tea.[27] Tea is well known in many biological systems for its antioxidant properties.[28] Nonetheless, few studies have linked polyphenol compounds in teas to preventive and antimicrobial therapeutic effects on certain ocular diseases.[29,30] Yang *et al*.[31] reported that green tea extract Theaphenon-E and its catechin components effectively reduce significant and permanent sodium iodide harm to the retina. Also, Theaphenon-E and its component catechins were found to have a significant protective effect against oxidative stress-induced outer retinal degeneration in the same study. The authors went on to suggest that green tea extract could be used to treat ocular diseases involving degeneration of the retinal pigment epithelium and photoreceptor cells. Similarly, Ren *et al*.[32] found that orally administered green tea extract had a significant anti-inflammatory effect on the retina after inflammation was exacerbated by lipopolysaccharides. This finding supports green tea extract's significant anti-inflammatory activity in subsequent eye segments during acute inflammation mediated by lipopolysaccharides. Obviously, the majority of studies on general effects of tea consumption have primarily focused on green tea and/or its extracts. On the other hand, almost no studies on the effects of black tea, particularly on retinal microcirculation, have been conducted using the newly available OCTA technology. As a result, the authors of this study embarked on this perilous journey to unravel the mystery of the black tea–microcirculation interrelationship.

Limitations of this study included a small study population and the use of a single tea variety. More studies with a much larger population, various types of tea forms such as green and/or white, different techniques of tea brewing and different amounts of fluid will therefore be worthwhile. Since this study only included data from healthy individuals of Turkish descent, there was no assessment of the effects of black tea based on race. Prior studies reported racial differences in foveal composition.[33,34] Additional studies are therefore needed to determine whether this study's findings apply to other races. Furthermore, caffeine and alcohol consumption prior to the study were not questioned, and only one OCTA device was used in this study, with the results interpreted based on this device.

CONCLUSIONS

By using OCTA, this study demonstrated for the first time that consumption of black tea, a fermentation product of *Camellia sinensis* leaves, does not induce acute retinal or macular morphological changes in healthy individuals. Nonetheless, larger clinical studies using more tea and/or different forms of teas, as well as a larger study population with a diverse range of racial groups, could yield more accurate results.

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Mustafa Dogan: project administration, conceptualization, methodology, software; Hamidu Hamisi Gobeka: methodology, data curation, writing–reviewing and editing; Mubera Akdogan: visualization, investigation, methodology; Anar Alizada: formal analysis, visualization, investigation; Mehmet Cem Sabaner: formal analysis, visualization, investigation; Ozgur Erogul: validation, visualization, formal analysis; Mehmet Akif Seylan: validation, visualization, writing–original draft preparation; Furkan Fatih Gulyesil: validation, visualization, writing–original draft preparation.

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