• Clinical Research •

Chronic alcohol consumption on retinal microcirculation in healthy subjects: an optic coherence tomography angiography study

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Abstract

● **AIM:** To investigate the effects of chronic alcohol consumption on retinal microcirculation by comparing different alcohol-consuming groups using optical coherence tomography (OCT) and OCT angiography (OCTA).

● **METHODS:** This observational clinical study utilized a cross-sectional and prospective design, focusing on chronic alcohol consumers alongside a non-consuming control group. OCT/OCTA imaging parameters including central retinal subfield thickness (CST), subfoveal choroidal thickness (SCT), foveal avascular zone (FAZ) and vessel density (VD) in the superficial and deep capillary plexuses in both the macular and optic disc (OD) regions were recorded. Data were analyzed using SPSS 15.0; descriptive statistics were reported, group comparisons were performed with Chi-square, Kruskal–Wallis, and Bonferroni-corrected Mann–Whitney *U* tests, and relationships were assessed using Spearman correlation, with statistical significance set at $P<0.05$.

● **RESULTS:** A total of 160 eyes of 160 participants (110 females and 50 males with mean age 38.7±9.9y) who don't smoke were divided into five groups: never, occasional, monthly, weekly and daily drinkers. The mean CST was 216.6±14.2 μm and the mean SCT was 358.9±84.5 μm. There was no statistically significantly difference in CST and SCT among the groups (P=0.890, 0.799). Foveal superficial capillary plexuses (SCPs) VD was higher in monthly drinkers compared to occasional drinkers (P=0.015). Foveal VD in deep capillary plexus was also higher in monthly drinkers than in never and occasional drinkers (P=0.004, 0.006). Nasal SCPs VD at the OD was higher in monthly drinkers compared to never drinkers (P=0.005). There was no significant difference FAZ area among the groups (P=0.071).

● **CONCLUSION:** Both superficial and deep microvascular structures in the inferior quadrants of macula are positively correlated with frequency of alcohol use. Also in our study results is that the monthly drinker group has uniquely higher VDs in both macula and OD. This leads us to consider moderate alcohol consumption may also have protective effects on retinal microcirculation.

● **KEYWORDS:** alcohol consumption; foveal avascular zone; retinal microcirculation; optical coherence tomography angiography; vessel density

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INTRODUCTION

Alcohol consumption is a notable public health concern and the data shows that it will increase in the future[1]. Numerous studies have shown that heavy alcohol consumption is linked to a higher risk of all-cause mortality and various life-threatening conditions[2]. These arise not only from the macrovascular effects of alcohol but also from its influences on the smaller vessels. Chronic alcohol intake can lead to increase vasodilation, inflammation, ischemia and altered blood flow dynamics which damage the endothelial cells of the retinal microcirculation[3].

The vasculature of the retina involves a complex network of tiny blood vessels, including capillaries, arterioles, and venules. This network is essential for maintaining retinal health, as it provides oxygen and nutrients, eliminates waste products, and supports the overall function of retinal neurons. The retina is particularly sensitive to fluctuaions in blood flow and perfusion, rendering it susceptible to systemic health issues[4].

Optical coherence tomography angiography (OCTA) is a non-invasive imaging method that offers high-resolution images with a broad field of view and significant depth of retinal and choroidal vessels. OCTA detects fluctuations in signal amplitude caused by the movement of blood cells relative to surrounding static tissues. Unlike traditional dye-based angiography, OCTA enables rapid acquisition of high-resolution images that provide detailed information on retinal and choroidal circulation[5]. OCTA delivers essential data for early diagnosis, highlighting retinal vascular parameters like vessel density (VD), tortuosity, and flow velocity as important biomarkers[6]. Utilizing these quantitative measures, we can identify the microvascular effects of alcohol on the retina through OCTA.

Previous studies have examined the acute influence of alcohol consumption on retinal vascularization before. In the most recent one, Zhuang *et al*[4] utilized OCTA to investigate acute effect of heavy alcohol consumption on choroidal and retinal vasculature, and their findings were a significant decrease in choroidal and choroidal vessel volume and an increase in choroidal capillaris density, but no significant differences in retinal vascular parameters. According to these results, they defended that alcohol causes choroidal arteriolovenular vasoconstruction but choroidal capillary vasodilation.

To the best of our knowledge, although acute impact of heavy alcohol consumption on retinal vasculature is studied before, chronic effects remain underexplored. Due to the absence of similar research, we aimed to compare alcohol-consuming groups with varying frequencies, through OCTA analysis to investigate the impact of chronic alcohol use on retinal microcirculation.

PARTICIPANTS AND METHODS

Ethical Approval All participants consisted of individuals who visited the outpatient clinic for routine eye examinations. The study received ethical approval from the Ethics Committee at Prof. Dr. Cemil Tascioglu City Hospital (approval ID: 237220208) and adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

This observational clinical study utilized a cross-sectional and prospective design, focusing on chronic alcohol consumers alongside a non-consuming control group. A total of 160 eyes from 160 participants were included, both eyes were scanned but to avoid inter-eye correlation, only one eye per participant was included in the analysis; the right eye was selected to ensure consistency and comparability across participants.

Alcohol consumption was assessed through interviews conducted during examination. Interviewers asked participants if they have ever consumed alcohol and how often they have drank during the last year. Based on their responses, participants were classified as never, occasional, monthly, weekly, or daily drinkers. Occasional drinking was defined as consuming alcohol less than once in a month, while monthly consuming was one to three times per month and weekly drinking was categorized as one to three times per week. Daily drinking referred to consuming alcohol four or more times per week. A drink, according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), is one 12-ounce bottle of wine cooler or beer, one 5-ounce glass of wine, or 1.5 ounces of 80-proof distilled liquor. Based on this information, data on the type of alcohol consumed was not queried and a drink was defined as 5 ounces of wine. All subjects were selected from individuals who do not smoke.

Each participant underwent a comprehensive ophthalmic assessment, which included evaluations of best-corrected visual acuity (BCVA), anterior segment biomicroscopy, intraocular pressure (IOP) measured with a Goldmann applanation tonometer, fundus examination, and swept-source optical coherence tomography (SS-OCT) and OCTA scans performed with DRI-Triton® (Topcon Corporation, Tokyo, Japan).

Patients were excluded from the study if they had any pathologies or systemic conditions such as diabetes, hypertension *etc*. affecting the anterior or posterior segment, refractive errors greater than ±1 D spherical equivalent, prior ocular trauma or surgery or chronic ocular conditions (such as glaucoma, uveitis or optic atrophy). Those with poor-quality optical coherence tomography (OCT) or OCTA scans were also excluded.

The OCTA device has an axial resolution of 8 μm, a transverse resolution of 20 μm, and captures 100 000 A-scans per second. OCT images were obtained while the subjects focused on a fixed point after pupil dilation, with images showing a signal power density greater than 40 included in the study.

For macular measurements, a 6 mm×6 mm area was selected in “angio macular” mode, automatically centered on the fovea, while optic disc (OD) measurements required manual centering on the optic nerve head. VD was calculated as the ratio of vessel area exhibiting blood flow to the total measured area, with assessments made in five quadrants: central (foveal and papillary), superior, inferior, nasal, and temporal, using the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. For macular and radial peripapillary capillary (RPC) VD measurements, four layers were automatically segmented in each subarea: superficial capillary plexus (SCP) and deep capillary plexus (DCP). Papillary VD was measured only in the superficial and deep layers. The SCP extends from 2.6 μm below the internal limiting membrane to 15.6 μm below the inner plexiform layer, while the DCP spans from 15.6 to 70.2 μm below the inner plexiform layer.

Table 1 Demographic factors

Items	Frequency of alcohol consumption					*P*
	Never	Occasional	Monthly	Weekly	Daily	
Age (y), mean±SD	41.2±9.8	37.8±9.5	27.8±3.9	34.8±8.7	40.7±12.1	0.027
Gender, *n* (%)	40 (25)	40 (25)	24 (15)	36 (22.5)	20 (12.5)	0.253
Female	30 (75.0)	33 (82.5)	17 (70.8)	20 (55.5)	10 (50)	
Male	10 (25.0)	7 (17.5)	7 (29.2)	16 (45.5)	10 (50)	
Intraocular pressure (mm Hg)	16.2±2.5	15.7±2.2	15.8±0.8	16.8±2.9	14.0±3.0	0.534

SD: Standard deviation.

The OCT and SS-OCTA results were evaluated and documented by two independent experienced researchers , with patient information kept confidential. Average measurements for the foveal avascular zone (FAZ) area and subfoveal choroidal thickness (SCT) were calculated from both observers for statistical analysis. Interobserver and intraobserver correlations for FAZ SCP-DCP were examined, with interobserver variability assessed using statistical comparison (*P*=0.183, *P*=0.165 respectively, Student's *t*-test). Intraobserver variability was measured using the coefficient of variation (CV), calculated as CV=SD/mean×100%. The first observer's CV ranged from 34% to 33%, while the second observer's ranged from 37% to 35%. Similar evaluations were conducted for SCT, with interobserver variability assessed (*P*=0.212, Student's *t*-test), and intraobserver variability determined (CVs of 31% for the first observer and 34% for the second).

The FAZ area boundary was manually outlined using a caliper, with the device's automatic calculation method utilized for area determination. SCT measurements were also taken manually under the fovea, referencing the border of the sclera (total choroidal thickness).

The SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics were provided as frequency and percentage for categorical variables, and mean, standard deviation, minimum, and maximum for numerical variables. The Chi-square test was used to compare proportions between independent groups. Since the normality assumption was not met for numerical variables, comparisons of more than two independent groups were performed using the Kruskal-Wallis test. Posthoc analyses were conducted with the Mann-Whitney *U* test and interpreted using the Bonferroni correction. Relationships between numerical variables were examined using Spearman's correlation analysis, as parametric test assumptions were not met. The statistical significance level was set at $P<0.05$.

RESULTS

The study contains 160 eyes of 160 patients. Table 1 presented demographic factors of the study sample. The mean age was 38.7±9.9y and a statistically significant difference was found between the mean ages of the groups (*P*=0.027). This difference showed that the age of the monthly drinker group was statistically significantly lower than that of the never drinkers (*P*=0.004). There was no statistically significant difference in gender ratios or IOPs between the groups, nor was there a statistically significant correlation between the patients' IOPs and the frequency of alcohol use (*P*=0.534).

The mean central subfield thickness (CST) was 216.6±14.2 μm and the mean SCT was 358.9±84.5 μm. There was no statistically significantly difference between the groups (*P*=0.890, *P*=0.799). However a statistically significant positive correlation was found between CST and age (*P*=0.015). Also it was detected that for the mean macular VD results, there was a negative correlation between superior and inferior SCP-DCP and age (*P*=0.003, *P*=0.001 *P*=0.018, *P*=0.013) while IOP had a negative correlation with FAZ and inferior DCP and a positive correlation with foveal SCP VD (*P*=0.011, *P*=0.049, *P*=0.049).

When macular VD results are compared according to the frequency of alcohol consumption, it was found that there was a statistically significantly difference between the groups only for foveal SCP (*P*=0.046; Table 2). That difference was due to foveal SCP VD values being higher in monthly drinkers than in occasional drinkers (*P*=0.015). However, a borderline statistically significant difference was detected in foveal DCP VD (*P*=0.050). It was found higher in monthly drinkers than in never drinker and occasional drinker groups (*P*=0.004, *P*=0.006). And also, there were significant positive correlations between the inferior SCP and DCP and the frequency of alcohol use (*P*=0.040, *P*=0.042). Nevertheless, there was no significant difference between the FAZ area of the groups (*P*=0.071).

According to the radial peripapillary capillary VDs of the OD, a significant difference between the group was detected simply for nasal SCP (*P*=0.031; Table 3). It was found higher in monthly drinkers than in never drinker group (*P*=0.005). There was no significant correlation between the frequency of alcohol use and OD VD results, when it was examined with Spearman correlation analysis.

DISCUSSION

The study of Bray *et al*[7] has examined the age trend in alcohol

Table 2 The macular VD measurements of the groups mean±SD

Items	Frequency of alcohol consumption					*P*
	Never	Occasional	Monthly	Weekly	Daily	
FAZ area, μm^2	344.3±123.7	373.9±125.0	205.2±43.9	321.5±148.0	293.6±125.2	0.071
CST, μm	215.7±13.6	216.5±16.2	215.2±16.7	219.5±15.4	221.0±8.9	0.890
SCT, μm	356.0±78.2	353.8±73.9	389.0±119.1	374.9±115.4	315.3±30.3	0.799
SCP VD, %						
Foveal	19.0±5.5	17.7±3.9	24.8±2.1	20.2±5.3	20.7±5.0	0.046
Superior	48.5±2.9	48.9±1.9	48.7±1.0	48.1±2.0	46.0±3.5	0.542
Temporal	46.7±2.2	47.2±2.3	46.7±1.5	47.3±1.3	47.4±1.3	0.878
Inferior	47.5±3.4	48.0±2.9	46.6±6.5	49.3±1.5	49.8±1.7	0.318
Nasal	45.8±1.9	45.9±2.3	45.0±2.3	45.4±2.0	43.6±3.3	0.737
DCP VD, %						
Foveal	15.0±3.7	14.9±3.3	20.0±1.9	16.4±4.9	15.2±4.9	0.050
Superior	49.9±3.6	49.9±1.6	49.0±4.2	49.3±2.2	43.0±10.0	0.552
Temporal	47.1±2.2	47.2±3.5	47.9±3.5	47.0±2.3	47.2±1.8	0.841
Inferior	49.3±3.4	49.4±1.4	49.0±1.9	50.6±2.2	52.1±1.1	0.082
Nasal	46.6±2.3	45.9±2.5	45.8±1.0	47.4±1.9	47.2±3.1	0.204

VD: Vessel density; SD: Standard deviation; FAZ: Foveal avascular zone; CST: Central subfield thickness; SCT: Subfoveal choroidal thickness; SCP: Superficial capillary plexus; DCP: Deep capillary plexus.

Table 3 The mean radial peripapillary capillary VD measurements of the groups mean±SD

Items	Frequency of alcohol consumption					*P*
	Never	Occasional	Monthly	Weekly	Daily	
SCP peripapillary VD, %						
Central	13.9±8.6	14.2±10.8	7.9±5.2	8.6±7.9	22.7±14.3	0.121
Superior	78.3±87.5	65.9±2.5	66.2±2.6	114.0±167.3	58.4±4.3	0.070
Temporal	55.3±10.2	51.7±14.3	56.3±3.1	58.1±5.3	49.2±7.4	0.294
Inferior	66.9±4.9	67.0±3.7	70.1±3.2	67.1±1.3	62.8±3.4	0.144
Nasal	61.3±7.5	64.3±4.7	69.0±3.2	59.9±11.3	60.6±1.4	0.031
DCP peripapillary VD, %						
Central	38.2±13.6	38.6±12.5	31.6±15.8	32.0±15.4	42.4±10.7	0.582
Superior	47.4±7.8	45.5±7.3	46.9±4.1	50.2±8.3	40.8±21.6	0.656
Temporal	48.9±5.8	49.2±6.7	52.9±2.3	50.8±4.0	44.2±4.3	0.081
Inferior	48.6±7.1	47.0±6.8	43.9±1.9	50.5±10.5	45.6±14.5	0.270
Nasal	51.5±8.1	52.5±8.1	47.0±5.2	50.3±10.8	48.8±17.5	0.453

VD: Vessel density; SD: Standard deviation; SCP: Superficial capillary plexus; DCP: Deep capillary plexus.

use patterns in US in 2019. The results represented that the ratio of non-drinkers was 22% at age18-24y, but 64% at age 65y; when the extreme drinkers were at 32% at age 22y and 1% at age 65y. In the same study, males were found to be less likely be non- and frequent light drinkers and more likely to be frequent heavy episodic and extreme drinkers. Meanwhile similarly in our study, the age of the monthly drinker group was statistically significantly lower than that of the never drinkers. On the other hand, there was no difference between the sex of the groups.

In a 9-year retrospective cohort study consisting of 825 eyes from the USA published in 2023, the associations of alcohol consumption and smoking with the development of glaucoma were investigated. According to this study, patients who developed glaucoma had a higher history of smoking, higher alcohol consumption, lower mean IOP[8]. However alcohol consumption was found to be related to ocular hypertension by Leske *et al*[9] in 1996. In our study, we could not find any relationship between the IOP and the frequency of alcohol consumption.

In an OCT study conducted in 2020 with 211 healthy Mexican individuals, the mean age was 34.3±11.9y and the mean CST was 227.4±18.9 μm[10]. In our study they were 38.7±9.9 and 216.6±14.2 μm respectively. Although they have found no significant correlation between CST and age, we found a positive correlation between them. Another study from India,

with 308 eyes; CST measures were 246.55±18.73 μm under age 30y, 252.41±21.68 μm between 30 and 50y, 263.01±20.55 μm above age 50y, thickening with age like our study results[11].

According to a prospective and cross-sectional study in healthy subjects, age and the mean macular SCP VD results were negatively correlated for the all foveal, nasal, superior, inferior and temporal quadrants[12]. Whereas by our results, there was a negative correlation between superior and inferior SCP-DCP and age.

To the best of our knowledge, effects of chronical alcohol consumption on retinal microcirculation has not been studied before. Nevertheless, there are some studies about acute effects. Dhasmana *et al*[13] studied the effects of acute oral ethanol consumption on the retinal circulation in diabetic and non diabetic patients and no change in retinal blood velocity as assessed with laser Doppler velocimetry was observed. In 2009, Luksch *et al*[14] investigated the effects of intravenously administered ethanol on retinal vessel diameters with retinal vessel analyzer and the results showed that retinal arterial diameters increased after administration but no significant change was observed on retinal veins. A more recent study researched the acute impact of heavy alcohol intake by OCTA. The evaluation parameters were choroidal volume, choroidal vessel volume, choroidal capillaries density and retinal VD. Choroidal and choridal vessel volume significantly decreased after spirits and wine consumption; conversely, choroidal capillaries density had a significant increase. However the changes in retinal VD were not statistically significant, and no difference was found between this two types of alcohol's effects on ocular microvasculature[4].

In our research, we explored the impact of chronic alcohol consumption on retinal vascularisation alterations. For the purpose of evaluating this, we utilized OCTA to assess the VD in different segments of the macula and OD. For macular scan segments, deep retina inferior quadrant had the highest mean VD. These results suggest that normal subjects exhibit higher blood perfusion in the deeper layers of the macula compared to the superficial layers, consistent with findings from previous studies[15-16]. Possibly; as a result of this increased perfusion, the present study found positive correlations between the frequency of alcohol use and the inferior SCP and DCP.

The foveal SCP and DCP VD were both higher in monthly drinker group than from groups with less frequent alcohol use. This may be related to the lower mean age of this group. In some studies that comparing the smokers and non-smokers' macular perfusion by OCTA, the enlargement of the FAZ area and the reduction of the foveal DCP VD were noticed in the smoker group[17-18]. This led us to hypothesize that the ischemic effects of smoking are more pronounced than those of alcohol. In a study by 20 patients with methanol poisoning they found that foveal SCP VD decreased in patients with methanol toxicity, but there were no significant changes in foveal DCP, peripapillary, and inside disc VD. On the other hand, there was a significant decrease in inner retinal thickness, which can be a reason for the lower foveal SCP VD[19].

Kojima *et al*[20] investigated acute effects of ethanol effects on optic nerve head blood flow and revealed a significant increase in optic nerve head blood flow. Otherwise, the retinal nerve fiber layer (RNFL) was found thinner in alcohol use disorder patients before[21]. Although we detected no significant correlation between the frequency of alcohol use and OD VD results, the radial peripapillary nasal SCP results were higher in monthly drinkers than in never drinkers.

Many previously published studies showed that moderate alcohol consumption is associated with lower cardiovascular disease risk[22]. Excessive or drinking undoubtedly results in higher morbidity and mortality rates.

Observational studies have consistently reported that alcohol intake is positively associated with an elevated risk of atrial fibrillation, heart failure, and hemorrhagic stroke, suggesting a detrimental effect of alcohol on certain cardiovascular outcomes. In contrast, moderate alcohol consumption has been linked with a lower risk of coronary heart disease and ischemic stroke[23]. One potential mechanism through which alcohol consumption may increase the risk of cardiovascular disease (CVD) is *via* its effects on blood pressure. Elevated blood pressure is a well-established risk factor for multiple CVD outcomes, and evidence suggests that alcohol may exert a dose-dependent hypertensive effect. A Meta-analysis of randomized controlled trials demonstrated that reductions in alcohol intake were associated with significant decreases in blood pressure, particularly among individuals consuming more than two alcoholic drinks per day, supporting a causal relationship between heavy alcohol use and hypertension-related cardiovascular risk[24].

Furthermore, particularly alcoholic beverages high in polyphenols, like wine and beer, appear to offer cardiovascular protective benefits in patients. Moderate red wine consumption provides this effect through some changes it makes in the body. It reduces platelet aggregation by decreasing tissue factor, fibrinogen, factor VII and von Willebrand factor and protects endothelial cells by decreasing endothelin-1 and increasing nitric oxide and flow-mediated dilation. It also raises adinopectin, apolipoprotein-1, high-density lipoprotein, insulin sensitivity and plasma antioxidant capacity when reducing C-reactive protein and oxidative DNA damage[25-26]. What is noteworthy in our study results is that the monthly drinker group has uniquely higher VDs in both macula and OD. This led us to consider moderate alcohol consumption may also have protective effects on retinal microcirculation.

Our study has several limitations. First of all, our subject size is limited and the sample size per group was not equal. The reason for this might be that alcohol consumption was assessed through self-report, which may have resulted in underestimation of intake due to social desirability bias. A cross-sectional analysis was conducted using data from the Canadian Longitudinal Study on Aging (CLSA) Comprehensive Cohort. The study included 30 097 adults aged 45 to 85y. Alcohol consumption frequency was categorized as never (2.4%), occasional (40.2%), weekly (41.3%), and daily (16.1%); as in our study, the group distribution was not equal. The type of alcohol consumed (red wine, white wine, beer, spirits, and other) was assessed using an interviewer-administered questionnaire, and total alcohol intake (grams per week) was estimated[27]. Unfortunately, data on the type and amount of alcohol is not recorded in our study because this exhibited considerable day-to-day variability. In line with the National Institutes of Health (NIH) definitions, we defined one drink unit as 5 ounces of wine, as this was the beverage most frequently consumed by our patients[28]. Future research should aim to more precisely characterise the dose–response relationship between alcohol consumption and retinal microcirculation. In addition, the absence of data on caffeine or sodium intake and physical activity may have contributed to residual confounding. Besides, the manual measurements of OCTA may not be considered reliable; to overcome this issue, the mean values collected by two different experienced observers and the interobserver variability was calculated. Automated measurements could provide more accurate values. In conclusion, we demonstrated that the both superficial and deep microvascular structures in the inferior quadrants of macula were positively correlated with frequency of alcohol use. Furthermore more comprehensive studies are needed to shed light on the changes on retinal microcirculation of chronical alcohol consumption.

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