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EVALUATION OF RETINAL MICROVASCULAR ALTERATIONS IN SMOKERS WITHOUT SYSTEMIC DISEASE USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Purpose: To evaluate retinal microvascular alterations in chronic smokers without systemic comorbidities using optical coherence tomography angiography (OCTA) and to assess the relationship between smoking exposure and retinal microvascular parameters.

Methods: This prospective cross-sectional observational study included 40 chronic smokers (≥2 pack-years) without systemic disease. All participants underwent comprehensive ophthalmic examination and OCTA imaging using a 6×6 mm macular scan and a 4.5×4.5 mm optic nerve head scan. Quantitative parameters analyzed included superficial capillary plexus (SCP) vessel density, deep capillary plexus (DCP) vessel density, foveal avascular zone (FAZ) area, radial peripapillary capillary (RPC) density, and ganglion cell complex (GCC) thickness. Correlation between smoking exposure (pack-years) and OCTA parameters was assessed using Pearson correlation analysis.

Results: The mean SCP and DCP vessel densities were 44.3 ± 3.8% and 46.1 ± 4.1%, respectively. The mean FAZ area was 0.39 ± 0.08 mm². The mean RPC density and GCC thickness were 50.2 ± 4.5% and 89.6 ± 6.2 µm, respectively. Smoking exposure demonstrated a significant negative correlation with SCP vessel density ($r = -0.52$, $p < 0.001$) and DCP vessel density ($r = -0.47$, $p < 0.001$), while FAZ area showed a significant positive correlation ($r = 0.44$, $p < 0.001$).

Conclusion: Chronic smoking is associated with measurable retinal microvascular alterations detectable by OCTA, even in the absence of systemic disease. Increasing smoking exposure correlates with reduced vessel density and enlargement of the FAZ, suggesting early microvascular compromise. OCTA may serve as a sensitive, non-invasive tool for detecting subclinical smoking-related vascular injury.

Keywords: Smoking; optical coherence tomography angiography; retinal microvasculature; vessel density; foveal avascular zone; pack-years

Introduction

Cigarette smoking remains one of the leading preventable causes of morbidity and mortality worldwide and is a well-established risk factor for systemic vascular disease[1,7]. The harmful effects of tobacco smoke are mediated through complex mechanisms including oxidative stress, endothelial dysfunction, chronic inflammation, and impaired nitric oxide bioavailability[1,9]. These pathophysiological processes result in widespread microvascular injury, ultimately contributing to cardiovascular, cerebrovascular, and peripheral vascular diseases.

The retinal microvasculature represents a unique and accessible model for studying systemic microcirculation in vivo. Owing to its anatomical and physiological similarities with cerebral and coronary microvasculature, the retina serves as a surrogate marker for systemic vascular health[8]. Retinal vascular changes have been shown to precede clinically apparent systemic disease, thereby providing an opportunity for early detection of microvascular dysfunction.

Chronic exposure to tobacco smoke has been associated with alterations in vascular tone, increased blood viscosity, and impaired autoregulation of blood flow[9,10]. In the ocular context, smoking has been implicated in the pathogenesis of several diseases, including age-related macular degeneration, retinal vascular occlusions, and optic neuropathies[12,16]. However, these associations are often confounded by coexisting systemic conditions such as diabetes and hypertension, which independently affect retinal microvasculature.

Optical coherence tomography angiography (OCTA) has emerged as a revolutionary imaging modality that enables non-invasive, depth-resolved visualization of retinal and choroidal microvasculature without the need for dye injection[2,3]. OCTA provides quantitative metrics such as vessel density of the superficial capillary plexus (SCP) and deep capillary plexus (DCP), foveal avascular zone (FAZ) area, and radial peripapillary capillary (RPC) density, which serve as reliable biomarkers of retinal perfusion and microvascular integrity[4,6]. Compared to conventional imaging modalities, OCTA offers superior sensitivity in detecting early microvascular changes, even in the absence of clinically visible fundus abnormalities.

Emerging evidence suggests that smoking may lead to subtle but measurable alterations in retinal microvasculature detectable by OCTA[6,14]. Reduced vessel density, impaired perfusion, and enlargement of the FAZ have been reported in smokers, indicating early microvascular compromise. However, most available studies include subjects with systemic comorbidities or established ocular disease, thereby limiting the ability to isolate the independent effect of smoking on retinal microcirculation.Furthermore, the dose–response relationship between smoking exposure and retinal microvascular parameters remains inadequately explored. Quantification of smoking burden using pack-years provides an objective measure to assess cumulative exposure and its impact on microvascular health. Understanding this relationship is essential for identifying early biomarkers of smoking-induced vascular injury.In this context, the present study aims to evaluate retinal and optic nerve head microvascular alterations in smokers without systemic disease using OCTA and to analyze the correlation between smoking exposure and quantitative microvascular parameters. By focusing on a relatively healthy population, this study seeks to delineate early subclinical microvascular changes attributable to smoking alone, which may have important implications for early detection, risk stratification, and preventive interventions.

MATERIALS AND METHODS

Study Design and Ethical Approval

This **prospective cross-sectional observational study** was conducted in the Department of Ophthalmology at **R.L. Jalappa Hospital and Research Centre**, affiliated with Sri Devaraj Urs Medical College, Kolar, India, over a period from **January 2025 to April 2026**. The study was initiated after obtaining approval from the Institutional Ethics Committee, and all procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Inclusion Criteria
- Age between **30–60 years**
- History of smoking ≥ **2 pack-years**
- Best-corrected visual acuity (BCVA) ≥ **6/9**
- Clear ocular media permitting high-quality imaging
- Willingness to provide informed consent

Exclusion Criteria
- Any **ocular pathology** (e.g., glaucoma, diabetic retinopathy, age-related macular degeneration)
- **Systemic diseases** affecting microvasculature (diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease)
- History of **ocular surgery or trauma**
- Refractive error > ±3 diopters
- Poor-quality OCTA images (signal strength index < 7)

Data Collection Procedure
Clinical Evaluation
All participants underwent a detailed evaluation including:
- Best-corrected visual acuity (BCVA) assessment
- Slit-lamp biomicroscopy
- Intraocular pressure measurement using Goldmann applanation tonometry
- Dilated fundus examination

Smoking History Assessment
A structured questionnaire was used to document:
- Type of smoking (cigarette/bidi/mixed)
- Duration of smoking (years)
- Number of cigarettes per day

Pack-years were calculated as:
Pack-years = (Cigarettes per day × Years smoked) / 20
OCTA Imaging Protocol
OCTA imaging was performed using a **spectral-domain OCTA device (Cirrus AngioPlex, Carl Zeiss Meditec, Dublin, CA, USA)**.
Scan protocols:
- **6 × 6 mm macular scan**
- **4.5 × 4.5 mm optic nerve head scan**

Only images with **adequate segmentation and signal strength ≥ 7** were included.

Parameters Analyzed
Macular Microvasculature
- Superficial capillary plexus (SCP) vessel density (%)
- Deep capillary plexus (DCP) vessel density (%)
- Foveal avascular zone (FAZ) area (mm²)

Optic Nerve Head Parameters
- Radial peripapillary capillary (RPC) density (%)
- Ganglion cell complex (GCC) thickness (μm)

Outcome Measures
- **Primary Outcome:**
  - Retinal microvascular changes (vessel density) on OCTA
- **Secondary Outcome:**

- Correlation between smoking exposure (pack-years) and OCTA parameters

Sample Size Calculation

The sample size was calculated to detect a **moderate correlation (r = 0.45)** between smoking exposure and OCTA parameters with **95% confidence** and **80% power**, yielding a minimum sample size of **36 participants**. Considering a 10% non-response rate, the final sample size was set at **40 participants**.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation. Descriptive statistics and correlation analysis were performed. Pearson correlation analysis was used to assess associations between pack-years and OCTA parameters. A p-value < 0.05 was considered statistically significant.

Results

1. Baseline Characteristics

Table 1: Demographic and Clinical Characteristics

Parameter	**Value (n=40)**
Age (years)	34.8 ± 6.5
IOP (mmHg)	14.8 ± 2.3
Pack-years	11.2 ± 5.6

"The mean age of participants was 34.8 ± 6.5 years. The mean intraocular pressure was within normal limits. The mean smoking exposure was 11.2 ± 5.6 pack-years."

2. OCTA Parameters

Table 2: Retinal and Optic Nerve Head OCTA Parameters

Parameter	**Mean ± SD**
SCP Vessel Density (%)	44.3 ± 3.8
DCP Vessel Density (%)	46.1 ± 4.1
FAZ Area (mm²)	0.39 ± 0.08
RPC Density (%)	50.2 ± 4.5
GCC Thickness (μm)	89.6 ± 6.2

"The mean superficial and deep capillary plexus vessel density values were 44.3 ± 3.8% and 46.1 ± 4.1%, respectively. The mean FAZ area was 0.39 ± 0.08 mm². Optic nerve head analysis showed a mean RPC density of 50.2 ± 4.5% and GCC thickness of 89.6 ± 6.2 μm."

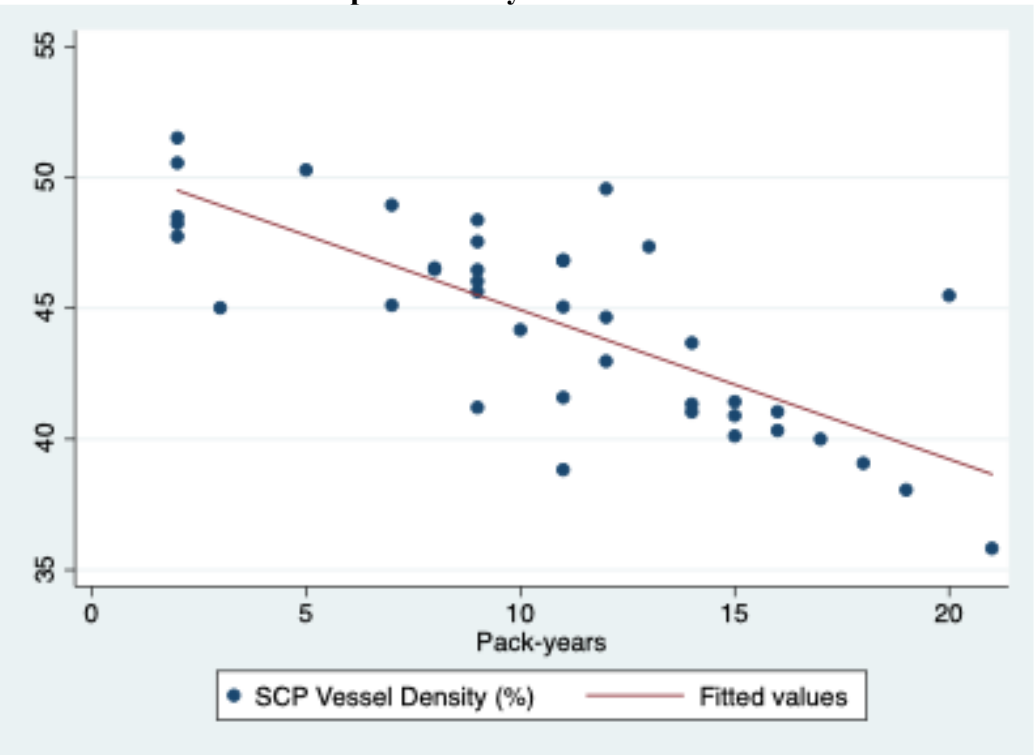
3. Correlation Analysis

Table 3: Correlation Between Smoking Exposure and OCTA Parameters

Parameter	**Correlation (r)**	**p-value**
SCP VD	−0.52	<0.001
DCP VD	−0.47	<0.001
FAZ Area	+0.44	<0.001

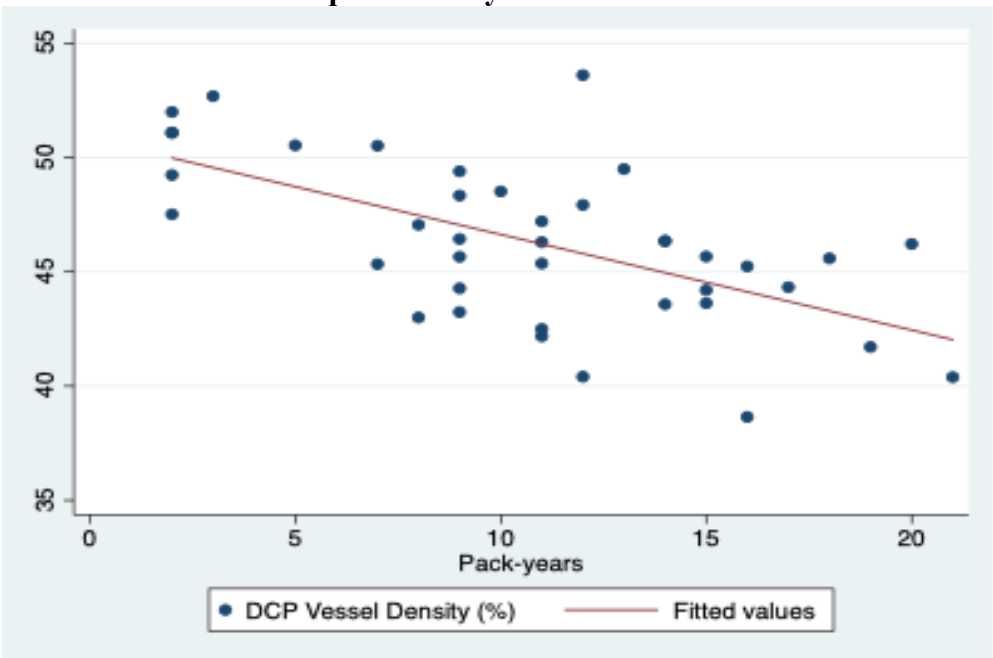
A significant negative correlation was observed between smoking exposure (pack-years) and vessel density parameters. In contrast, FAZ area showed a significant positive correlation with smoking exposure."

Graph 1: Pack-years vs SCP VD



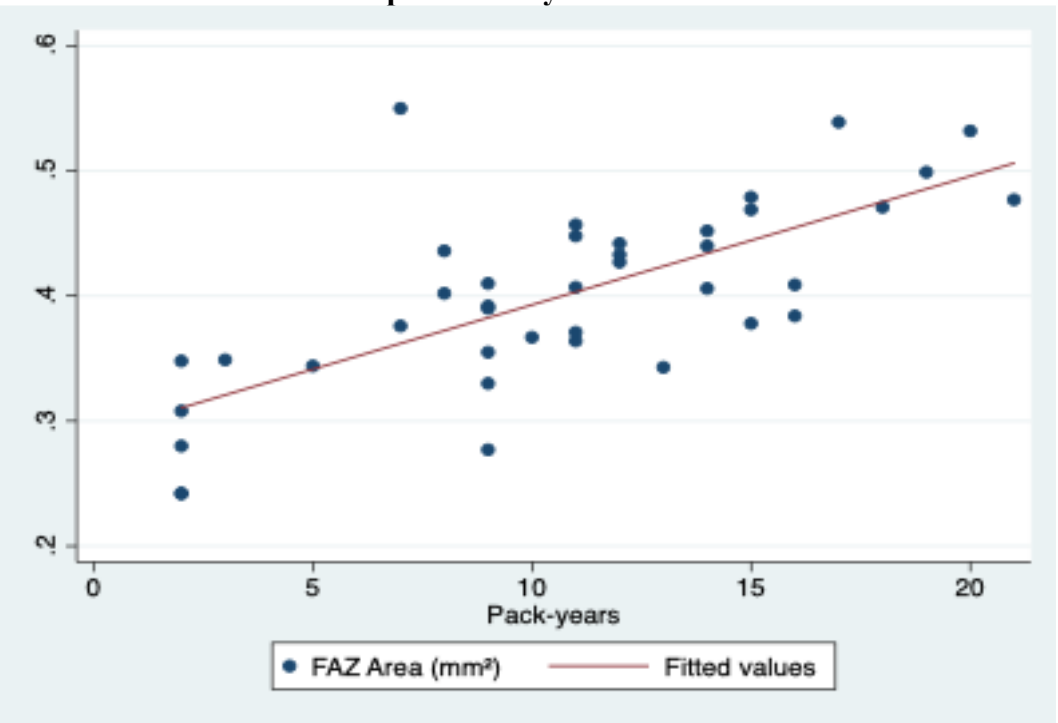
Scatter plot showing significant negative correlation between smoking exposure and SCP vessel density.

Graph 2: Pack-years vs DCP VD



Scatter plot demonstrating a negative correlation between smoking exposure (pack-years) and deep capillary plexus vessel density.

Graph 3: Pack-years vs FAZ



Scatter plot demonstrating a positive correlation between smoking exposure (pack-years) and foveal avascular zone (FAZ) area.

Discussion

The present study demonstrates a significant association between chronic smoking and retinal microvascular alterations, as evidenced by OCTA-derived parameters. A negative correlation was observed between smoking exposure (pack-years) and vessel density in both the superficial and deep capillary plexuses, while a positive correlation was noted with FAZ area. These findings indicate that increasing cumulative exposure to tobacco smoke is associated with progressive microvascular compromise, even in individuals without systemic disease.

The reduction in vessel density observed in this study can be attributed to the well-established effects of smoking on vascular endothelium. Tobacco smoke contains numerous reactive oxygen species and pro-inflammatory mediators that induce oxidative stress and endothelial dysfunction[1,7]. Endothelial injury leads to impaired vasodilation, increased vascular resistance, and reduced capillary perfusion. Additionally, nicotine exerts a direct vasoconstrictive effect and reduces nitric oxide availability, further compromising microvascular blood flow[1,9]. These mechanisms collectively contribute to capillary dropout and microvascular rarefaction, which are reflected as decreased vessel density on OCTA.

The deep capillary plexus (DCP) appears particularly susceptible to smoking-induced damage. The DCP is located in a watershed zone of retinal circulation and has a higher metabolic demand, making it more vulnerable to hypoxia and ischemia. The observed stronger negative correlation between pack-years and DCP vessel density supports the hypothesis that deeper retinal layers may be affected earlier or more severely in smoking-related microvascular injury. Similar observations have been reported in previous OCTA studies evaluating smokers and patients with systemic vascular conditions[13,14].

The enlargement of the FAZ with increasing smoking exposure further corroborates the presence of macular ischemia. The FAZ represents an area devoid of capillaries, and its enlargement reflects loss of perifoveal capillary integrity. Previous studies have demonstrated that FAZ enlargement is a sensitive indicator of early microvascular compromise in various retinal diseases[2,6]. In the present study, the positive correlation between pack-years and FAZ area suggests a dose-dependent

relationship between smoking and parafoveal ischemia, highlighting the cumulative impact of tobacco exposure on retinal perfusion.

The findings of this study are consistent with those of Moschos et al., who reported thinning of retinal and choroidal structures in chronic smokers[16]. Similarly, Aboud et al. demonstrated reduced macular and peripapillary vessel density using OCTA in smokers[14]. Zhang et al. further reported reduced retinal blood flow density using advanced OCTA analysis techniques[6]. However, unlike these studies, which included subjects with systemic comorbidities, the present study specifically excluded such confounding factors, thereby providing stronger evidence for the independent effect of smoking on retinal microvasculature.An important strength of this study is the focus on a relatively healthy population without systemic disease. This allows for a more accurate assessment of smoking-related microvascular changes without the influence of confounding variables such as diabetes, hypertension, or dyslipidemia. The demonstration of significant microvascular alterations in this population underscores the direct and potentially early impact of smoking on retinal circulation.

The clinical implications of these findings are noteworthy. The retina serves as a readily accessible extension of the central nervous system and provides valuable insights into systemic microvascular health. Retinal vascular changes have been shown to correlate with cardiovascular and cerebrovascular risk[8]. Therefore, the identification of early retinal microvascular alterations in smokers may have broader implications for systemic disease risk stratification and prevention.

Furthermore, the ability of OCTA to detect subclinical changes before the onset of overt clinical manifestations highlights its potential role as a screening tool in high-risk populations. In smokers with otherwise normal ocular examination, OCTA may reveal early perfusion deficits that could prompt timely lifestyle modifications and preventive interventions.

Despite these strengths, the present study has certain limitations. The absence of a control group limits direct comparison with non-smokers and restricts the ability to quantify the magnitude of difference attributable to smoking. However, the use of correlation analysis with pack-years provides insight into the dose-dependent effects of smoking. The relatively small sample size and cross-sectional design also limit the ability to establish causality. Longitudinal studies with larger cohorts are required to evaluate the progression and reversibility of these microvascular changes. Additionally, factors such as axial length, environmental exposure, and passive smoking were not fully controlled and may have influenced the results.

Conclusion

Chronic smoking is associated with significant retinal microvascular alterations detectable by optical coherence tomography angiography, even in the absence of systemic disease. Increasing smoking exposure, as measured by pack-years, demonstrates a clear association with reduced vessel density in both superficial and deep capillary plexuses and enlargement of the foveal avascular zone, indicating early microvascular compromise.These findings suggest that smoking exerts a direct, dose-dependent deleterious effect on retinal microcirculation. The ability of OCTA to detect such subclinical changes highlights its potential as a sensitive, non-invasive tool for early identification of smoking-related microvascular injury.

Early recognition of these changes may aid in risk stratification and reinforce the importance of smoking cessation to prevent progression to overt ocular and systemic vascular disease. Further longitudinal studies with larger sample sizes and control groups are warranted to validate these findings and assess their clinical implications.

Disclosure

The authors report no conflicts of interest in this work.

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