RESEARCH PAPER

Retinal Microvascular Changes in Iron Deficiency Anemia Using Optical Coherence Tomography Angiography – A Case-Control Study

Sasankadhar Reddy M[1], Apoorva N[2*], Chaitra MC[3]

[1]Junior resident, Department of Ophthalmology, Sri Devaraj Urs Medical College, Kolar, Karnataka.

[2]Assistant professor, Department of Ophthalmology, Sri Devaraj Urs Medical College, Kolar, Karnataka.

[3]Professor, Department of Ophthalmology, Sri Devaraj Urs Medical College, Kolar, Karnataka.

[*]Corresponding author: Apoorva N

ABSTRACT

Background: Iron deficiency anemia (IDA) is the most common nutritional anemia worldwide and is associated with systemic hypoxia due to reduced hemoglobin levels. The retina and optic nerve head are highly metabolically active tissues with dense microvascular networks and are particularly vulnerable to alterations in oxygen delivery. Optical coherence tomography angiography (OCTA) is a non-invasive imaging modality that enables quantitative assessment of retinal and peripapillary microvasculature, allowing detection of subtle vascular changes that may not be clinically apparent.

Objectives: To evaluate retinal microvascular changes, including macular superficial and deep capillary plexus vessel density, radial peripapillary capillary vessel density, and foveal avascular zone parameters, in patients with iron deficiency anemia using OCTA, and to correlate these findings with hematological parameters.

Methods: This hospital-based case–control study included 37 patients with iron deficiency anemia and 37 age- and sex-matched healthy controls. All participants underwent detailed ophthalmic examination and OCTA imaging of the macula and optic disc. Vessel density parameters of the superficial capillary plexus, deep capillary plexus, and radial peripapillary capillaries, along with foveal avascular zone metrics, were analyzed. Hematological parameters including hemoglobin and iron profile were recorded. Statistical comparisons between groups and correlation analyses were performed.

Results: The IDA group demonstrated significantly altered retinal microvascular parameters compared with controls. Superficial and deep capillary plexus vessel densities were significantly higher in several macular regions in IDA patients, while foveal avascular zone area and perimeter showed no significant difference. Deep capillary plexus changes were more pronounced than superficial plexus alterations. Radial peripapillary capillary density showed limited sectoral differences. Significant positive correlations were observed between hemoglobin and vessel density parameters, whereas ferritin showed negative correlations.

Conclusion: Iron deficiency anemia is associated with significant retinal and peripapillary microvascular alterations, likely reflecting compensatory vascular responses to chronic systemic hypoxia. OCTA may serve as a useful non-invasive tool for early detection of microvascular changes related to iron deficiency anemia.

Keywords: Iron deficiency anemia; Optical coherence tomography angiography; Retinal microvasculature; Superficial capillary plexus; Deep capillary plexus; Radial peripapillary capillaries.

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INTRODUCTION:

Iron deficiency anemia (IDA) is the most prevalent nutritional deficiency worldwide and remains a major public health concern across all age groups and physiological states. According to the World Health Organization, anemia is defined by reduced hemoglobin concentration below age- and sex-specific thresholds, resulting in impaired oxygen delivery to tissues and subsequent systemic dysfunction[1]. Beyond its well-recognized hematological manifestations, iron deficiency has been shown to adversely affect cellular metabolism, mitochondrial function, and tissue oxygenation, contributing to neurological, cognitive, and behavioral deficits[2].

The retina, characterized by high metabolic demand and dense microvascular architecture, is particularly vulnerable to systemic hypoxic and ischemic insults. Advances in retinal imaging have enabled detailed evaluation of retinal structure and perfusion in systemic diseases. Optical coherence tomography angiography (OCTA) is a non-invasive imaging modality that provides depth-resolved visualization of retinal and optic nerve head microvasculature without the need for dye injection[3]. OCTA allows quantitative assessment of the superficial capillary plexus (SCP), deep capillary plexus (DCP), radial peripapillary capillary (RPC) network, and foveal avascular zone (FAZ), thereby offering insight into microvascular alterations associated with systemic conditions.

Previous studies using conventional OCT have demonstrated reduced macular thickness, altered choroidal thickness, and changes in peripapillary retinal nerve fiber layer (RNFL) thickness in patients with iron deficiency anemia[4–11]. More recent investigations have extended these observations to OCTA-based metrics, reporting altered retinal vessel density and microvascular remodeling in various anemic states[13,14]. However, existing literature remains heterogeneous, with inconsistent findings regarding the direction and magnitude of vascular changes, particularly across different retinal layers and regions[12].

Furthermore, limited studies have explored the relationship between retinal microvascular parameters and specific hematological indices such as hemoglobin, serum iron, ferritin, transferrin saturation, and total iron-binding capacity. Understanding these associations is essential to elucidate the pathophysiological link between systemic iron status and retinal microcirculation.

The present study aims to comprehensively evaluate FAZ characteristics, SCP, DCP, and RPC vessel density parameters in patients with iron deficiency anemia using OCTA and to correlate these microvascular changes with hematological parameters, thereby contributing to a more integrated understanding of retinal involvement in IDA.

MATERIAL AND METHODS:

This case–control study was conducted over a period of 12 months at the Department of Ophthalmology, R. L. Jalappa Hospital, Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants in their vernacular language prior to enrolment

A total of 74 participants were included in the study, comprising 37 patients with iron deficiency anemia (IDA) and 37 age- and sex-matched healthy controls. Patients aged 18–60 years with a clinical and hematological diagnosis of iron deficiency anemia were recruited for the case group. IDA was defined as hemoglobin levels <12 g/dL in females or <13 g/dL in males, along with low serum ferritin and/or low serum iron with elevated total iron-binding capacity. Healthy individuals without anemia and with normal hematological parameters served as controls.

Participants with systemic conditions known to affect retinal or optic nerve circulation, such as diabetes mellitus, hypertension, renal disease, or other hematological disorders, were excluded. Additional exclusion criteria included a history of glaucoma, uveitis, dense cataract, significant refractive error (>±3.00 diopters spherical equivalent), ocular trauma, prior ocular surgery, pregnancy or lactation, use of medications affecting retinal or choroidal blood flow, and prior treatment for anemia.

All participants underwent a comprehensive ophthalmological evaluation, including best-corrected visual acuity assessment, slit-lamp biomicroscopy of the anterior segment, intraocular pressure measurement using non-contact tonometry, and fundus examination with indirect ophthalmoscopy and a +90D lens. Hematological data, including hemoglobin concentration and iron profile parameters, were obtained from laboratory reports.

Optical coherence tomography angiography was performed using the CIRRUS HD-OCT Model 5000. Macular scans (6 × 6 mm) and optic disc scans (4.5 × 4.5 mm) were acquired for both eyes. Parameters analyzed included superficial capillary plexus and deep capillary plexus vessel density, radial peripapillary capillary vessel density, foveal avascular zone area, and peripapillary retinal nerve fiber layer thickness. Only scans with a signal strength index of 6 or higher and without motion or segmentation artifacts were included in the analysis. All investigation-related expenses were borne by the principal investigator. Data were entered into Microsoft Excel and analyzed using SPSS version 22. Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as frequencies and proportions. Intergroup comparisons were performed using Student’s t-test for normally distributed variables and Mann–Whitney U test for non-normally distributed data. Categorical variables were analyzed using the Chi-square test or Fisher’s exact test as appropriate. A p value <0.05 was considered statistically significant.

RESULTS:

The comparison of hematological parameters between the two groups revealed statistically significant differences. The iron deficiency anemia (IDA) group exhibited significantly lower mean hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin values when compared with the control group. In contrast, red cell distribution width was significantly higher in the IDA group, reflecting increased anisocytosis. These findings are characteristic of microcytic hypochromic anemia and confirm the hematological distinction between the study groups (Table 1).

Analysis of foveal avascular zone parameters demonstrated no statistically significant difference between the IDA and control groups with respect to FAZ area or FAZ perimeter. However, superficial capillary plexus vessel density in the whole image was significantly higher in the IDA group. Regional assessment showed a significant increase in parafoveal SCP vessel density among IDA subjects, particularly within the inferior hemi-parafoveal and inferior parafoveal sectors. Vessel density measurements in the foveal, other hemi-field, and perifoveal regions did not demonstrate statistically significant intergroup differences (Table 2).

Deep capillary plexus analysis revealed significantly higher vessel density in the IDA group compared with controls in the whole image, superior hemi, and inferior hemi regions. Parafoveal DCP vessel density was also significantly increased in the IDA group, with statistically significant differences observed in the superior hemi, superior, and nasal sectors. In the perifoveal region, significantly higher vessel density was noted in the superior hemi, temporal, superior, and nasal sectors among IDA subjects, whereas foveal and inferior sector measurements were comparable between the two groups (Table 3).

Evaluation of optic disc parameters showed no statistically significant difference in overall peripapillary retinal nerve fiber layer thickness between the groups. Sectoral analysis demonstrated a statistically significant difference only in the superior RNFL quadrant. Radial peripapillary capillary vessel density parameters did not differ significantly between the IDA and control groups in whole image, inside disc, or most sectoral analyses, with the exception of a statistically significant difference observed in the superior hemi RPC vessel density (Table 4).

Correlation analysis within the IDA group demonstrated statistically significant positive correlations between hemoglobin concentration and SCP whole, DCP whole, and RPC whole vessel densities. Transferrin saturation, total iron-binding capacity, and serum iron levels also showed significant positive correlations with SCP, DCP, and RPC vessel densities. In contrast, serum ferritin levels exhibited statistically significant negative correlations with SCP, DCP, and RPC whole vessel density. No statistically significant correlation was observed between FAZ area and any of the hematological parameters (Table 5).

Scatterplot analysis illustrated a positive association between mean hemoglobin concentration and vessel density in both the superficial capillary plexus and radial peripapillary capillary networks, indicating that higher hemoglobin levels are associated with increased retinal and peripapillary microvascular density (Fig. 1).

Table 1: Comparison of hematologic parameters between groups.

	IDA group (n =37)		Control group (n =37)		P value
	Mean	SD	Mean	SD	
Hb (g/dL)	12.94	.20	8.14	1.88	<0.001*
Hct (%)	40.34	2.75	30.47	4.51	0.007*
MCV (fL)	87.68	2.49	70.25	7.31	<0.001*
MCH (pg)	29.30	1.42	19.82	3.27	0.001*
RDW (%)	11.73	.17	18.10	2.65	<0.001*

Table 2: Comparison of FAZ and SCP vessel density parameters.

	IDA group (n =37)		Control group (n =37)		P value
	Mean	SD	Mean	SD	
FAZ area (mm^2)	.27	.05	.26	.07	0.091
FAZ Perimeter (mm^2)	2.15	.38	2.03	.35	0.810
FD (%)	56.36	2.60	53.41	4.57	0.001*
Whole image	52.56	2.44	48.18	2.76	0.447

Superior-Hemi	52.32	2.50	46.71	2.76	0.485
Inferior-Hemi	52.72	2.46	47.45	3.38	0.061
Fovea	20.83	5.42	16.43	5.03	0.354
Parafovea	55.10	2.70	49.35	4.15	0.047*
Superior-Hemi	55.64	2.80	49.15	3.71	0.237
Inferior-Hemi	54.27	2.53	47.35	5.17	0.002*
Temporal	53.85	3.26	49.14	3.51	0.628
Superior	56.20	3.33	49.36	4.21	0.278
Nasal	53.41	3.44	48.31	4.12	0.274
Inferior	55.26	2.17	48.01	4.59	0.002*
Perifove	53.04	2.06	47.83	2.43	0.195
Superior-Hemi	53.00	2.46	46.75	3.40	0.104
Inferior-Hemi	52.69	2.46	47.40	2.65	0.307
Temporal	49.37	2.43	45.14	3.18	0.229
Superior	53.27	2.37	47.83	3.29	0.072
Nasal	56.37	2.04	49.76	2.51	0.320
Inferior	53.27	2.72	47.48	2.74	0.626

Table 3: Comparison of DCP vessel density parameters.

	IDA group (n =37)		Control group (n =37)		P value
	Mean	SD	Mean	SD	
Whole image	55.44	3.45	47.93	8.47	0.001*
Superior-Hemi	56.20	5.02	49.02	7.09	0.02*
Inferior-Hemi	56.20	5.60	49.76	8.94	0.019*
Fovea	38.01	7.03	35.08	7.19	0.745
Parafovea	58.28	3.39	55.07	5.84	0.004*
Superior-Hemi	57.75	3.21	53.90	5.11	0.015*
Inferior-Hemi Temporal	58.38	3.83	52.88	4.88	0.222
Superior	58.13	4.04	53.71	6.20	0.011*
Nasal	58.31	3.01	54.40	5.28	0.041*
Inferior	57.28	3.60	52.54	5.14	0.270
Perifovea	59.19	4.30	53.19	4.71	0.292
Superior-Hemi	58.41	3.58	52.94	6.46	0.001*
Inferior-Hemi	57.05	6.18	49.29	7.39	0.519
Temporal	57.09	4.61	51.18	6.88	0.035
Superior	56.51	5.34	52.44	9.29	0.001*
Nasal	59.15	3.75	52.44	7.54	0.001*
Inferior	56.16	6.34	49.25	7.25	0.669

IDA: Iron deficiency anemia, DCP: Deep capillary plexus

Table 4: Comparison of optic disc parameters between groups.

RNFL thickness	IDA group (n =37)		Control group (n =37)		P value
	Mean	SD	Mean	SD	
Peripapillary	121.72	11.90	113.30	11.78	0.751
Superior	132.95	14.49	134.18	21.58	0.013*
Temporal	77.43	8.15	77.13	10.17	0.103
Inferior	150.60	15.59	147.22	19.76	0.067
Nasal	106.21	14.95	111.41	18.11	0.686
RPC density	49.52	2.34	47.54	2.04	0.456
Whole image	52.74	2.84	51.23	3.69	0.119
Inside disc	50.64	3.48	48.44	2.86	0.564
Peripapillary	50.65	3.16	49.28	2.87	0.564
Superior-hemi	49.30	7.69	49.71	2.73	0.001*
Inferior-hemi	49.39	3.58	48.36	3.39	0.829
Superior	53.69	4.49	54.72	3.52	0.141
Temporal	52.41	3.62	51.61	3.36	0.379
Inferior	48.74	3.02	47.11	3.36	0.600
Nasal	121.72	11.90	113.30	11.78	0.751

IDA: Iron deficiency anemia, RNFL: Retina nerve fiber layer, RPC: Radial peripapillary capillary, * Mann Whitney U test was used to compare groups those not normally distributed.

Table 5: Correlation analysis of OCTA parameters with hematological parameters in IDA

		FAZ area	SCP whole	DCP whole	RPC whole
Hemoglobin (g/dL)	r	0.002	0.648	0.463	0.499
	p	0.983	0.001	0.001	0.001*
Transferrin saturation (%)*	r	0.154	0.507	0.305	0.356
	p	0.191	0.001	0.008	0.002*
TIBC (ug/dL)	r	0.05	0.623	0.549	0.406
	p	0.673	0.001	0.001	0.001*
Serum iron (ug/dL)*	r	0.085	0.568	0.315	0.357
	p	0.469	0.001	0.006	0.002*
Ferritin (ng/mL)	r	−0.084	−0.589	−0.480	−0.332
	p	0.474	0.001	0.001	0.004*

DCP: Deep capillary plexus, FAZ: Foveal

avascular zone, RPC: Radial peri- papillary capillary, SCP: Superficial capillary plexus, TIBC: total iron-binding capacity. * Spearson analysis was used to compare groups those not normally distributed.

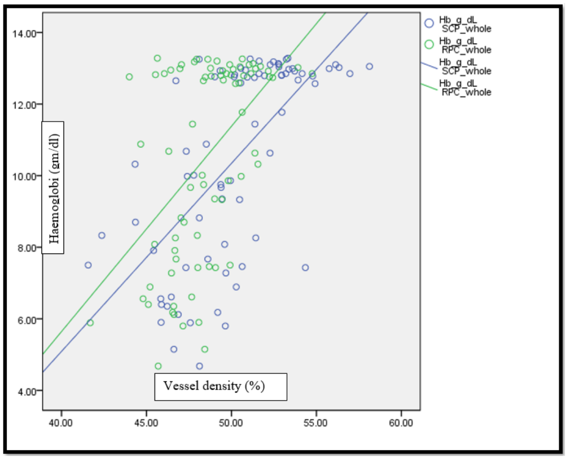

Fig. 1. Relationship between superficial capillary plexus (SCP) whole and radial peripapillary capillary (RPC) whole vessel density and mean hemoglobin. Scatterplot showing positive correlations between the mean hemoglobin and vessel density.

DISCUSSION:

The present study demonstrates significant alterations in retinal and peripapillary microvasculature in patients with iron deficiency anemia, while FAZ dimensions remain largely preserved. Hematological analysis confirmed classical features of microcytic hypochromic anemia, consistent with WHO diagnostic criteria[1].

FAZ area and perimeter did not differ significantly between groups, suggesting relative preservation of central foveal avascular architecture in IDA. Similar findings have been reported in OCTA-based studies where FAZ parameters appeared less sensitive to systemic anemia compared to vessel density indices[13,14]. This may reflect effective autoregulatory mechanisms maintaining foveal perfusion despite systemic hypoxia.

In contrast, SCP vessel density was significantly increased in the IDA group, particularly in the parafoveal and inferior sectors. These findings align with emerging evidence that chronic anemia may induce compensatory retinal vasodilation and capillary recruitment to counteract reduced oxygen-carrying capacity[13]. The absence of significant changes in foveal SCP density further supports region-specific vascular adaptation.

DCP analysis revealed more extensive and consistent increases in vessel density across whole image, hemi-fields, and parafoveal regions. The DCP is highly sensitive to metabolic stress due to its location within the inner nuclear layer, which may explain the pronounced microvascular response observed. Similar deep plexus alterations have been documented in systemic anemia and pregnancy-associated anemia using OCTA[14].

Optic disc evaluation showed largely preserved RNFL thickness, with only sectoral variation in the superior quadrant. Prior OCT-based studies have reported inconsistent RNFL changes in IDA, ranging from thinning to preservation[6,9–11,15]. The relatively stable RNFL parameters in the present study may indicate early or compensatory stages of microvascular involvement rather than overt neurodegeneration.

Correlation analysis revealed strong positive associations between SCP, DCP, and RPC vessel density with hemoglobin, serum iron, transferrin saturation, and TIBC, while ferritin showed significant negative correlations. These findings underscore the close relationship between systemic iron status and retinal microvascular regulation, supporting the hypothesis that retinal perfusion dynamically adapts to systemic oxygen availability[12,13].

Overall, the results suggest that iron deficiency anemia is associated with compensatory microvascular remodeling rather than ischemic rarefaction, particularly within the deep retinal capillary plexus.

CONCLUSION:

The present study demonstrates that iron deficiency anemia is associated with significant alterations in retinal and peripapillary microvascular parameters as assessed by optical coherence tomography angiography. While foveal avascular zone dimensions remained largely unaffected, vessel density in the superficial and deep capillary plexuses and radial peripapillary capillaries showed significant changes, suggesting compensatory microvascular remodeling in response to reduced oxygen-carrying capacity. The strong correlations observed between OCTA parameters and hematological indices further highlight the influence of systemic iron status on retinal microcirculation. OCTA may therefore serve as a valuable non-invasive tool for detecting early microvascular changes in iron deficiency anemia.

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