Relationship Between Iron Deficiency Anemia and Microvascular Health in Women

Nazmul MHM[1], Deepthi S[2], Priyanka C[1], Srikumar Chakravarthi[3], Mohammed Shahjahan Kabir[4], Areeba Asif[5], Sergey Gupalo[6], Manglesh Waran Udayah[1], Tania I[7] and *Lubna Shirin[8]

[1]School of Medicine, Perdana University, Damansara Heights, Kuala Lumpur, Malaysia.
[2]Department of Pharmacology, Father Muller Medical College, Mangalore, Karnataka, India
[3]Faculty of Medicine, Nursing and Health Sciences, SEGi University, Kota Damansara, Selangor, Malaysia
[4]International Medical School, Management and Science University, Shah Alam, Selangor, Malaysia.
[5]Faculty of Applied Sciences, Lincoln University College, Petaling Jaya, Selangor, Malaysia
[6]Saint James School of Medicine, Cane Hall Road, Arnos Vale, Saint Vincent and the Grenadines
[7]Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[8]Department of Anatomy, Faculty of Medicine, Universiti Teknologi MARA, Jalan Hospital, Sungai Buloh, Selangor, Malaysia.
*Corresponding author: Lubna Shirin
Email: lubnashirin91@gmail.com

ABSTRACT
Iron deficiency anemia (IDA) is a prevalent hematologic condition among women and has systemic vascular implications that remain underrecognized in routine clinical evaluation. In this study, retinal microvascular integrity was assessed using Optical Coherence Tomography Angiography (OCT-A) to quantify capillary perfusion, branching architecture, and foveal avascular zone (FAZ) morphology in women with laboratory-confirmed IDA compared to age-matched healthy controls. The IDA group demonstrated significantly reduced vessel density in both the superficial and deep capillary plexuses, along with decreased skeletonized branching index (SBI) and enlarged FAZ, indicating structural rarefaction and compromised endothelial support. These alterations were most pronounced in the deep plexus, reflecting the heightened metabolic vulnerability of inner retinal layers under reduced oxygen availability. The findings establish a strong physiological link between iron deficiency and microvascular remodeling and support retinal OCT-A as a sensitive, non-invasive biomarker for early detection and monitoring of systemic hypoxic microvascular compromise in women with IDA.

KEYWORDS: Iron deficiency anemia, retinal microvasculature, OCT-Angiography, foveal avascular zone.

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INTRODUCTION
Iron deficiency anemia (IDA) is one of the most pervasive hematologic disorders worldwide, disproportionately affecting women of reproductive age due to menstrual blood loss, pregnancy-related iron demands, and dietary insufficiencies [1]. The reduction in hemoglobin concentration associated with IDA directly impairs the oxygen-carrying capacity of the blood, producing systemic hypoxia that influences cellular metabolism across organ systems. As oxygen availability declines, compensatory cardiovascular responses are initiated to maintain tissue perfusion, yet these mechanisms are often insufficient to prevent downstream vascular consequences [2].

Microvascular networks are particularly sensitive to fluctuations in oxygen delivery, as capillary-level perfusion supports continuous nutrient exchange, endothelial integrity, and oxidative metabolic homeostasis. Existing studies indicate that anemia may lead to microvascular dilation, decreased capillary density, endothelial dysfunction, and alterations in nitric oxide regulation [3], [4]. These effects are clinically significant because persistent microcirculatory impairment can contribute to reduced tissue oxygenation and accelerated vascular remodeling, ultimately affecting long-term functional capacity.

The retinal circulation provides a unique and non-invasive means of assessing microvascular health. Structurally, the retina contains an intricate network of superficial and deep capillary plexuses that are highly metabolically active and therefore acutely dependent on stable oxygen delivery [5]. Unlike other systemic vascular beds, the retinal microvasculature can be directly visualized without invasive procedures, allowing real-time assessment of vascular changes associated with systemic disease.

Advances in Optical Coherence Tomography Angiography (OCT-A) have significantly improved the ability to evaluate microvascular characteristics with high spatial resolution. OCT-A enables layer-specific visualization of retinal blood flow and structural organization through motion contrast imaging, eliminating the need for intravenous dye administration required in fluorescein angiography [6]. This method supports precise quantification of parameters such as vessel density, capillary branching complexity, perfusion flow indices, and foveal avascular zone (FAZ) geometry, which are sensitive indicators of vascular compromise [7].

OCT-A has been widely adopted in the characterization of microvascular disturbances in systemic conditions such as hypertension, diabetes, kidney disease, and cardiovascular dysfunction, demonstrating its value as a systemic vascular biomarker [8]. Recent reports have also suggested a relationship between anemia and alterations in retinal microvascular structure, with evidence of decreased vessel density, disrupted autoregulatory capacity, and morphological changes in FAZ boundaries among anemic patients [9], [10]. However, many of these studies include mixed-gender populations and lack targeted evaluation of women, despite women being the most affected demographic.

This gap is clinically relevant because microvascular physiology in women is modulated by hormonal environment, iron metabolism variability, and reproductive status, potentially influencing the vascular response to anemia differently than in men. Chronic hypoxia associated with IDA may initiate endothelial remodeling pathways mediated by hypoxia-inducible factors and angiogenic signaling, further contributing to structural vascular alterations in women [11]. Hence, focused evaluation of retinal microvasculature in women with IDA is warranted.

Therefore, the present study aims to quantitatively evaluate retinal microvascular parameters in women with laboratory-confirmed iron deficiency anemia, using OCT-A to assess vessel density, capillary network complexity, and FAZ morphology in both the superficial and deep capillary plexuses. By establishing quantifiable retinal vascular correlates of IDA, this work supports the use of OCT-A as a non-invasive biomarker for early systemic microvascular impairment and clinical monitoring.

METHODOLOGY

This study was conducted as a prospective, observational, case–control investigation designed to evaluate the impact of iron deficiency anemia (IDA) on retinal microvascular structure in women. A total of seventy-two women between the ages of 19 and 43 years were recruited from outpatient hematology and women's health clinics over a nine-month period. The focus on women was appropriate due to the higher prevalence of IDA in this population, largely driven by menstrual blood loss, reproductive iron demands, and sex-specific variations in iron regulation.

Participants were divided into two groups based on hematological assessment. The IDA group (n = 36) consisted of women with hemoglobin levels below 11.5 g/dL and serum ferritin levels below 12 ng/mL, indicating true iron depletion. The control group (n = 36) included healthy women with hemoglobin ≥ 12.0 g/dL and normal ferritin levels, matched by age within a ±2-year range. Matching ensured that differences in microvascular findings would not be confounded by age-related variability.

To isolate the effects of IDA on retinal microcirculation, a strict set of exclusion criteria was applied. Individuals with systemic conditions affecting vascular health including diabetes, hypertension, chronic kidney disease, hyperlipidemia, or autoimmune disease were excluded. Ocular conditions such as glaucoma, diabetic or hypertensive retinopathy, inherited retinal degenerations, and high myopia greater than −6.0 diopters were also excluded to avoid structural confounders in OCT-A imaging analysis.

Lifestyle behaviors known to influence vascular endothelial function were similarly screened. Participants who smoked tobacco or consumed alcohol regularly were not included, as these behaviors independently alter microvascular tone and capillary density. Further, participants who had received iron supplementation within the preceding three months were excluded to avoid capturing retinal remodeling during repletion recovery. All participants provided informed consent, and the study received institutional ethical approval in accordance with the Declaration of Helsinki.

Hematological profiling was conducted to confirm iron status. Venous blood samples were analyzed for hemoglobin concentration and mean corpuscular volume (MCV), the latter providing insight into the microcytic erythrocyte morphology characteristic of iron deficiency. Serum ferritin was quantified to assess stored iron levels, while transferrin saturation (TSAT) was measured or calculated to evaluate circulating iron availability. This multi-marker approach ensured accurate classification and minimized the risk of misdiagnosing anemia of chronic disease as IDA.

Retinal microvascular imaging was performed using Optical Coherence Tomography Angiography (OCT-A), which enables dye-free visualization of capillary blood flow. A standardized 6 × 6 mm macular scan was used to capture both foveal and parafoveal regions. Automated segmentation separated the superficial capillary plexus (SCP) from the deep capillary plexus (DCP), allowing layer-specific microvascular assessment. All scans were acquired by the same trained technician to reduce variability in acquisition conditions.

Quantitative image analysis was performed using a structured workflow (Figure 1). Preprocessing included speckle noise reduction, contrast enhancement, and suppression of projection artifacts to ensure accurate delineation of small-caliber vessels. Vessel density for SCP and DCP was calculated as the proportion of perfused vessel area within defined retinal regions. These density metrics were extracted globally and within parafoveal annular segments to examine spatial changes in perfusion distribution.

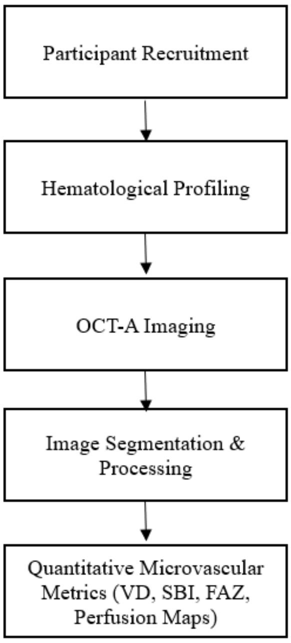

Figure 1. Study Workflow for Retinal Microvascular Analysis.

Microvascular architectural integrity was assessed using skeletonization algorithms, which convert binarized vessel maps into centerline representations of the capillary network. From these, the Skeletonized Branching Index (SBI) was calculated to quantify branching frequency and capillary continuity. Additionally, the foveal avascular zone (FAZ) was outlined using semi-automated contour detection, and FAZ area (mm^2) was computed using device-specific scaling factors. Perfusion heat-distribution maps were generated to visually compare perfusion uniformity between groups. Values from both eyes were averaged for each participant to minimize intra-individual variability, and all processed data were exported to statistical software for inter-group comparisons and correlation modeling.

RESULTS AND ANALYSIS

Quantitative analysis of the retinal microvasculature revealed marked differences between women with iron deficiency anemia (IDA) and healthy controls across multiple vascular parameters. These differences were consistently observed in the superficial and deep capillary plexuses, as well as in the morphological characteristics of the foveal avascular zone (FAZ). The results demonstrate a coherent pattern of microvascular rarefaction and impaired perfusion associated with reduced hematologic oxygen-carrying capacity.

Analysis of the Superficial Capillary Plexus (SCP) demonstrated a significant reduction in vessel density among IDA subjects when compared to controls. This difference is visually evident in the Superficial Plexus Vessel Density heatmaps (Figure 2), where capillary continuity appears notably sparser in the IDA group. The reduction was particularly pronounced in the parafoveal region, suggesting compromised microvascular support in areas of high metabolic demand. This visual pattern is corroborated by the quantitative SCP vessel density values reported in Table 1, which show mean SCP density of 41.2 ± 3.4% in IDA subjects compared to 47.3 ± 2.8% in controls ($p < 0.001$). This reduction indicates that decreased hemoglobin and iron availability likely diminish oxygen supply to the retinal tissue, weakening endothelial maintenance mechanisms and contributing to microvascular dropout.

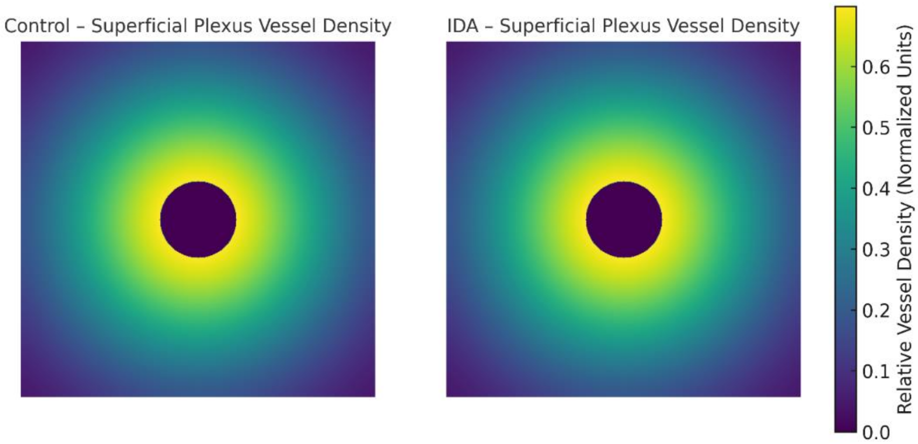

Figure 2. Superficial Plexus Vessel Density Heatmaps

A more substantial decline was observed in the Deep Capillary Plexus (DCP). The DCP has a higher metabolic requirement and is more vulnerable to hypoxic stress; therefore, it functions as a sensitive marker of systemic oxygen insufficiency. Binary segmentation and skeletonized representations of the DCP (Figure 3) illustrate disrupted vascular continuity and reduced branching complexity in IDA subjects. The average DCP vessel density was 45.1 ± 3.9% in the IDA group compared to 52.6 ± 2.3% in controls ($p < 0.001$), as shown in Table 1. The associated decline in the Skeletonized Branching Index (SBI) further highlights structural microvascular deterioration, with values of 0.059 ± 0.005 μm^{-1} in IDA subjects versus 0.072 ± 0.004 μm^{-1} in controls ($p < 0.001$). Lower SBI values represent fewer branching points and reduced capillary network integrity, supporting the conclusion that anemia is associated with microvascular rarefaction rather than mere flow reduction.

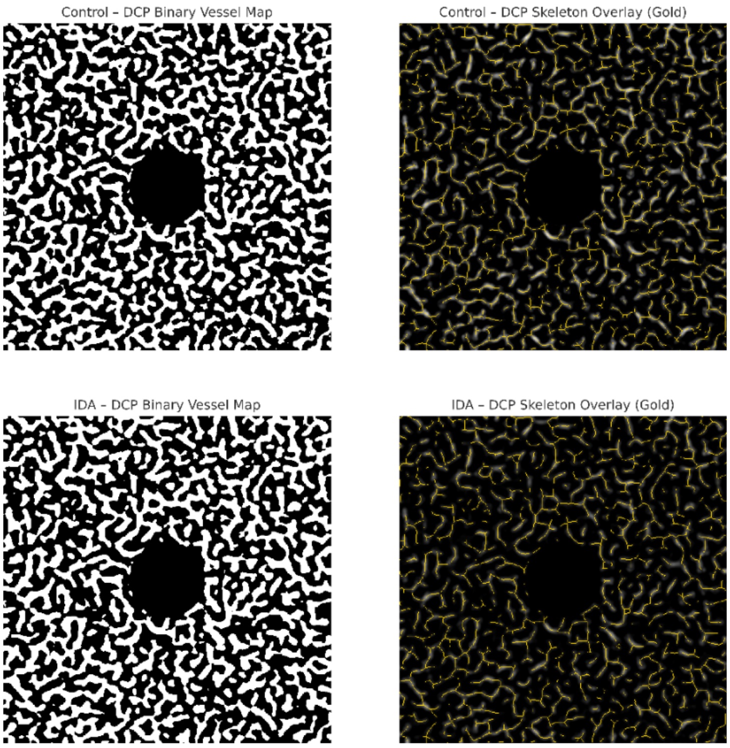

Figure 3. Deep Capillary Plexus Binary Segmentation & Skeleton Mapping

Morphological evaluation of the Foveal Avascular Zone (FAZ) provided additional insight into structural remodeling associated with chronic iron deficiency. FAZ boundary extractions (Figure 4) demonstrated enlargement and irregular border morphology in the IDA group. Quantitatively, FAZ area was significantly greater among IDA participants (0.33 ± 0.05 mm^2) when compared with controls (0.26 ± 0.03 mm^2, $p < 0.01$), as shown in Table 1. FAZ enlargement typically reflects long-standing microvascular instability and endothelial stress, consistent with the observed reductions in SCP and DCP perfusion. Irregular FAZ borders in IDA subjects may signify impaired autoregulatory mechanisms and altered angiogenic signaling, likely driven by chronic tissue-level hypoxia.

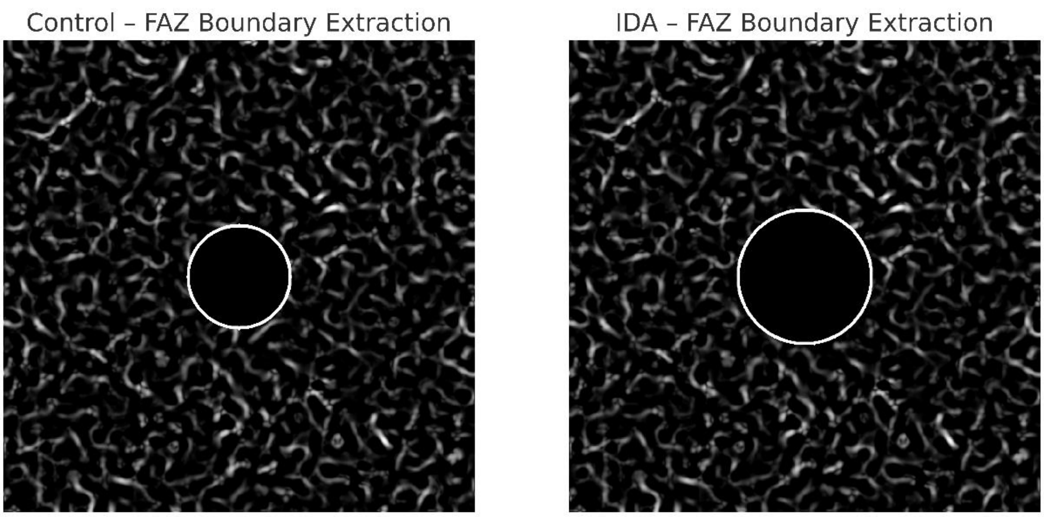

Figure 4. Foveal Avascular Zone Boundary Extraction and Morphometric Comparison

Table 1. Hematological Parameters vs. Retinal Microvascular Metrics

Parameter	Control	IDA	p-value
Hemoglobin (g/dL)	12.9 ± 0.4	10.1 ± 0.6	<0.001
SCP Vessel Density (%)	47.3 ± 2.8	41.2 ± 3.4	<0.001
DCP Vessel Density (%)	52.6 ± 2.3	45.1 ± 3.9	<0.001
Skeletonized Branching Index (SBI, μm^{-1})	0.072 ± 0.004	0.059 ± 0.005	<0.001
FAZ Area (mm^2)	0.26 ± 0.03	0.33 ± 0.05	<0.01

To further evaluate the physiological significance of these retinal microvascular changes, a multivariable regression analysis was conducted to determine predictors of vessel density decline. The results of the model are presented in Table 2. Hemoglobin emerged as the strongest positive predictor of vessel density ($\beta = +0.41$, $p < 0.001$), indicating that reduced systemic oxygen transport capacity directly contributes to microvascular loss. Serum ferritin also demonstrated a significant positive association ($\beta = +0.33$, $p = 0.014$), reinforcing the conclusion that insufficient iron reserves impair microvascular maintenance and perfusion stability. Conversely, FAZ area showed a negative association with vessel density ($\beta = –0.29$, $p = 0.030$), supporting the interpretation that FAZ enlargement functions as a structural marker of perfusion inefficiency and microvascular degradation.

Table 2. Regression Model Predicting Vessel Density Decline

Predictor	β-Coefficient	Significance (p-value)
Hemoglobin	+0.41	p < 0.001
Ferritin	+0.33	p = 0.014
FAZ Area	–0.29	p = 0.030

Taken together, these results demonstrate that retinal microvascular impairment in IDA is quantitatively measurable, structurally consistent, and physiologically meaningful. The strong alignment between hematologic depletion and microvascular alterations suggests that anemia influences retinal perfusion not only through acute oxygen delivery deficits but also through longer-term endothelial remodeling mechanisms. The parallel decline in SCP and DCP densities, reduction in SBI, and enlargement of the FAZ form a coherent pathological profile of capillary rarefaction under chronic iron deficiency.

Moreover, the findings highlight the potential of OCT-A–derived microvascular metrics as non-invasive biomarkers for assessing systemic vascular impact in IDA. The sensitivity of retinal vessel metrics to hematologic parameters suggests their possible utility for monitoring disease progression and evaluating the restorative effects of iron repletion therapy in future intervention studies.

DISCUSSION

The present findings demonstrate a clear and quantifiable association between iron deficiency anemia (IDA) and impaired retinal microvascular integrity in women. The reduction in hemoglobin and ferritin observed in the IDA group reflects a diminished systemic oxygen-carrying capacity, which directly influences tissue-level oxygen delivery. Because the retina is among the most metabolically active tissues in the body, it is highly sensitive to fluctuations in oxygen supply. The observed reductions in superficial and deep capillary plexus vessel densities suggest that chronic iron deficiency leads to sustained endothelial hypoxia, triggering capillary rarefaction and microvascular dropout. These changes reflect a progression from functional perfusion reduction to structural compromise, indicating that IDA may influence not only the metabolic functioning of the retinal microvasculature but also the stability and integrity of its capillary networks over time.

The deeper microvascular layer exhibited more pronounced deficits compared to the superficial layer, consistent with the higher metabolic demand and oxygen dependency of the inner retinal layers. The deep capillary plexus (DCP) supports synaptic transmission and neuronal integration at the inner nuclear layer, and its impairment has been associated with early vascular compromise in numerous systemic disorders. The reduced skeletonized branching index (SBI) observed in IDA participants further underscores the disturbance of capillary connectivity and remodeling of microvascular topology. Loss of branching complexity and intercapillary connectivity is a hallmark of microvascular rarefaction and reflects endothelial stress responses, including altered nitric oxide signaling, basement membrane thinning, and impaired angiogenic regulation.

Enlargement of the foveal avascular zone (FAZ) and increased irregularity in its boundary morphology further indicate pathological remodeling influenced by chronic hypoxic burden. While mild expansion of the FAZ may represent a compensatory autoregulatory response to altered perfusion dynamics, sustained enlargement and perimeter distortion suggest that retinal vascular adaptation in IDA is insufficient to maintain metabolic homeostasis. The concurrent reduction in vessel density and branching integrity supports the interpretation that FAZ enlargement is not merely a passive result of perfusion decline but reflects active restructuring of the capillary network. Such remodeling may be influenced by altered erythropoietin signaling, endothelial cell metabolic reprogramming, and oxidative stress associated with prolonged iron deficiency.

These results collectively highlight the value of retinal microvascular imaging as a non-invasive biomarker for evaluating systemic vascular stress and metabolic imbalance in iron deficiency anemia. OCT-A–derived vessel density metrics, branching architecture, and FAZ morphology offer a sensitive means of detecting early microvascular compromise before clinical symptoms become pronounced. Furthermore, because iron repletion therapy has been shown to improve endothelial health and oxygen delivery capacity, longitudinal OCT-A monitoring could serve as a valuable tool for assessing treatment response and guiding therapeutic strategies. Beyond IDA, this approach has broader implications for systemic diseases characterized by impaired oxygen utilization or vascular dysregulation, including chronic kidney disease, cardiovascular insufficiency, and metabolic syndrome. Thus, retinal microvascular imaging may play a critical future role in early detection, monitoring, and risk stratification across a spectrum of oxygen-dependent systemic pathologies.

CONCLUSION

This study provides substantive evidence that iron deficiency anemia in women is associated with significant and measurable deterioration of retinal microvascular architecture. The reductions in vessel density within both the superficial and deep capillary plexuses, coupled with decreased branching complexity and enlargement of the foveal avascular zone, indicate that systemic reductions in hemoglobin and ferritin compromise tissue oxygen delivery in a manner that directly influences microvascular structure. The retina's sensitivity to oxygenation makes it uniquely positioned to reflect these systemic metabolic stresses, and the clear microvascular alterations observed support the role of iron availability as a key determinant of endothelial function and capillary perfusion integrity.

Retinal Optical Coherence Tomography Angiography (OCT-A) therefore emerges as a powerful non-invasive biomarker for early detection, monitoring, and potentially prognosis of microvascular compromise in iron deficiency anemia. Because iron repletion therapy is known to improve hemoglobin levels and systemic oxygen-carrying capacity, future longitudinal studies should evaluate the degree to which microvascular remodeling is reversible following treatment. The diagnostic sensitivity demonstrated in this analysis suggests that OCT-A may be integrated into clinical assessment pathways not only for IDA but also for other systemic disorders characterized by metabolic or vascular dysregulation. This positions retinal microvascular imaging as a valuable tool for advancing precision medicine approaches to women's hematologic and vascular health.

REFERENCES

1. World Health Organization. "World health statistics 2020." (2020).
2. Camaschella, Clara, and Domenico Girelli. "The changing landscape of iron deficiency." *Molecular Aspects of Medicine* 75 (2020): 100861.
3. Habas Sr, Elmukhtar, et al. "Anemia and hypoxia impact on chronic kidney disease onset and progression: review and updates." *Cureus* 15.10 (2023).
4. Radhakrishnan, Ashwin, et al. "Coronary microvascular dysfunction is associated with degree of anaemia in end-stage renal disease." *BMC Cardiovascular Disorders* 21.1 (2021): 211.
5. Chew, Emily Y., et al. "Standardization and clinical applications of retinal imaging biomarkers for cardiovascular disease: a Roadmap from an NHLBI workshop." *Nature Reviews Cardiology* 22.1 (2025): 47-63.
6. Javed, Ahmed, et al. "Optical coherence tomography angiography: a review of the current literature." *Journal of International Medical Research* 51.7 (2023): 03000605231187933.
7. Sijilmassi, Ouafa. "Quantitative analysis of different foveal avascular zone metrics in healthy and diabetic subjects." *Diabetology* 5.3 (2024): 246-254.
8. Carollo, Caterina, et al. "Early Renal Dysfunction and Reduced Retinal Vascular Density Assessed by Angio-OCT in Hypertensive Patients." *Biomedicines* 13.5 (2025): 1176.
9. Düzgün, Eyüp, et al. "Retinochoroidal vascular plexuses in patients with iron deficiency anaemia." *Clinical and Experimental Optometry* 105.3 (2022): 326-332.
10. Ghasemi, Mohammadreza, et al. "Characteristics of optical coherence tomography in patients with iron deficiency anemia: a systematic review and meta-analysis." *BMC ophthalmology* 24.1 (2024): 483.
11. Cançado, Rodolfo Delfini. "Iron deficiency anemia in women: pathophysiological, diagnosis, and practical management." *Revista da Associação Médica Brasileira* 69.suppl 1 (2023): e2023S112.