International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Original Researcher Article *DOI: 10.61336/im/26-08-193*

Optical Coherence Tomography in Adult Patients of Iron Deficiency Anaemia: A Case–Control Study.

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Received: **18-07-2026**
Revised: **03-08-2026**
Accepted: **18-08-2026**
Published: **29-08-2026**

Abstract

Background: The retina is highly dependent on oxygen and iron for its structural and functional integrity. Iron deficiency has been linked to oligodendrocyte dysfunction, impaired myelination and retinal dopaminergic dysfunction, potentially affecting the retinal nerve fibre layer (RNFL) and macula. Optical coherence tomography (OCT) allows precise, non-invasive, micron-level measurement of these retinal structures. Objective: To study the ocular coherence tomography in adult patients of iron deficiency anaemia with haemoglobin less than 10.9 g/dl and compare them with healthy controls. ***Methods***: This case–control study enrolled 44 newly diagnosed adult patients of iron deficiency anaemia (IDA) (Hb < 10.9 g/dl, age 18–45 years) and 44 age- and sex-matched healthy controls at Pt. B.D. Sharma PGIMS, Rohtak, after ethical clearance and informed consent. Spectral-domain OCT (RTVue, Optovue Inc.) was used to record peripapillary retinal nerve fibre layer (RNFL) thickness (superior, inferior, nasal, temporal quadrants and average) and central macular thickness (CMT) in both eyes. Data were analysed on SPSS v20 using the unpaired Student's t-test, and Pearson's correlation coefficient was calculated between OCT parameters and the haemoglobin/iron profile. ***Results***: Mean haemoglobin was 7.25 ± 1.47 g/dl in cases versus 13.80 ± 1.30 g/dl in controls ($p < 0.0001$). Mean RNFL thickness in all quadrants (superior, inferior, nasal, temporal) and the average value were significantly reduced in both eyes of IDA patients compared with controls ($p < 0.0001$ for all comparisons). Central macular thickness was also significantly reduced in both eyes of cases compared with controls ($p < 0.0001$). Correlation of OCT parameters with haemoglobin and iron-profile indices was mild to moderate, with a moderate positive correlation between haemoglobin and central macular thickness in controls, and a moderate negative correlation between haemoglobin and nasal RNFL thickness in controls, in the left eye. ***Conclusion***: Adult patients of IDA show significant thinning of RNFL across all quadrants and of central macular thickness compared with healthy controls, indicating subclinical structural involvement of the visual pathway. OCT is a useful, non-invasive imaging tool for early detection and monitoring of ocular changes in iron deficiency anaemia.

Keywords: Iron deficiency anaemia; Optical coherence tomography; Retinal nerve fibre layer; Central macular thickness; Case–control study.

INTRODUCTION

Anaemia is a condition in which the number of red blood cells (RBCs) and, consequently, their oxygen-carrying capacity is insufficient to meet the body's physiological needs.[1] It affects an estimated 2.36 billion individuals globally, especially women and children.[2] The World Health Organization defines anaemia as a blood haemoglobin concentration below 13 g/dl in men and below 12 g/dl in women, and further classifies it as mild, moderate or severe according to the degree of haemoglobin reduction.[3] In India, national guidelines under the Anemia Mukt Bharat programme have adopted similar age- and sex-specific cut-offs to standardise screening and management across the population.[4] According to the National Family Health Survey-4 (NFHS-4), 58.4% of children aged 6–59 months, 53.1% of non-pregnant women, 50.3% of pregnant women and 22.7% of men aged 15–49 years were anaemic in India.[5] The aetiology of anaemia is multifactorial but is, for the most part, preventable, and includes inadequate dietary intake, poor living conditions and a high burden of infections such as malaria and intestinal parasitosis.[6]

Iron deficiency anaemia (IDA), the commonest nutritional cause of anaemia worldwide, is confirmed biochemically by a reduced serum iron and serum ferritin, an increased total iron binding capacity (TIBC) and a reduced transferrin saturation.[7] Because IDA in adults frequently has an insidious onset, the biochemical diagnosis is often delayed by months or years,

allowing time for iron-dependent tissues, including the central nervous system and the retina, to be affected well before the anaemia is recognised clinically.

The retina is one of the most metabolically active tissues in the body and requires a continuous, high level of oxygen and iron-dependent metabolic support to maintain its structural and functional integrity; changes in retinal vasculature and oxygen-carrying capacity that accompany chronic anaemia have even been proposed as a basis for using retinal imaging as a screening tool for anaemia.[8] Hypoxia and impaired retinal perfusion can lead to neuronal injury through several mediators, and retinal ganglion cells are particularly vulnerable to reduced perfusion and oxygen saturation.[8] Oligodendrocytes, crucial for myelination, require iron for normal function; certain iron-containing enzymes are concentrated in these cells, and a fall in iron availability during periods of active myelination can impair their function and, in turn, the integrity of structures dependent on normal axonal function, such as the retinal nerve fibre layer.[9,10] Iron deficiency has also been linked to retinal dopaminergic dysfunction, which is thought to alter the receptive area of axons and ganglion cells that constitute the retinal nerve fibre layer (RNFL).[11,12]

Optical coherence tomography (OCT) is a light-based, non-invasive imaging technique founded on the principle of low-coherence interferometry, providing high-resolution, in-vivo, cross-sectional images of retinal tissue.[13] Current OCT devices can resolve individual retinal layers and provide automated, reproducible measurements of retinal and peripapillary nerve fibre layer thickness to the nearest micron, and eye-tracking overlays allow detection of even minor longitudinal change, making OCT a powerful tool for both diagnosis and monitoring of diseases of the retina, optic nerve and macula.[14] A growing body of literature has examined RNFL and macular thickness on OCT in patients with iron deficiency anaemia, predominantly in children and women, and has generally reported significant thinning compared with healthy controls.[15,16] Because IDA in adults often has an insidious onset with diagnosis delayed by months or years, OCT being objective, reproducible and non-invasive offers a means of detecting subclinical retinal changes before overt ocular symptoms appear, providing the rationale for evaluating it in adult patients of IDA.[17]

MATERIALS AND METHODS

Study design and setting

This was a prospective, case–control study conducted in the Department of Physiology in collaboration with the Department of Medicine and the Regional Institute of Ophthalmology, Pt. B.D. Sharma PGIMS, Rohtak, after approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants in their own language before enrolment.

Study population

Subjects were divided into two groups:

- Group 1 (Cases): 44 newly diagnosed patients of iron deficiency anaemia (IDA) of either sex, aged 18–45 years, with haemoglobin < 10.9 g/dl, confirmed on serum iron studies.
- Group 2 (Controls): 44 age- and sex-matched healthy subjects.

Exclusion criteria: Chronic disorders (diabetes mellitus, cerebrovascular disease, Parkinsonism, multiple sclerosis, neuromuscular disorders, drug-induced neuropathy, smoking, alcoholism, malabsorption syndromes, chronic hepatic or renal disease); history of intake of drugs with known visual or neurotoxicity; history of loss of vision; altered sensorium or psychiatric illness; pregnancy; glaucoma or any macular pathology; and COVID-19-positive status at the time of testing.

Sample size

Sample size was calculated using the standard formula for comparison of means between two independent groups [$N = (Z_{1-\alpha/2} + Z_{1-\beta})^2(\sigma1^2 + \sigma2^2)/(\mu1 - \mu2)^2$], with $Z_{1-\alpha/2} = 1.96$ (95% confidence) and $Z_{1-\beta} = 0.84$ (80% power), yielding a minimum of 44 subjects per group (total N = 88).

Clinical and biochemical assessment

Detailed history, general physical examination, complete haemogram and iron profile (serum iron, serum ferritin, TIBC and transferrin saturation) were recorded for every subject on a pre-designed proforma.

Optical coherence tomography procedure

OCT was performed using a spectral-domain OCT system (RTVue, model RT100, Optovue Inc., Fremont, California; software v5.0) after pupillary dilatation with tropicamide eye drops. The subject was seated with the head resting on a fixed support to minimise movement and asked to fixate on the internal target of the device. Peripapillary RNFL thickness (superior, inferior, nasal, temporal quadrants and average) was recorded using the glaucoma protocol, and central macular thickness was recorded using the MM6 macular mapping scan (six radial line scans spaced 30° apart, centred on the fovea) in both eyes. Retinal thickness was recorded after inspecting the segmentation lines on individual scans.

Statistical analysis

Data were entered in Microsoft Excel and analysed using SPSS version 20. Continuous variables are expressed as mean ± SD and were compared between cases and controls using the unpaired Student's t-test. A p-value < 0.05 was considered statistically significant. Pearson's correlation coefficient (r) was calculated between the study parameters and haemoglobin/iron-profile indices; r < 0.3 was taken as mild, 0.3–0.5 as moderate, and r > 0.5 as strong correlation.

RESULTS

Eighty-eight subjects (44 cases, 44 controls) completed the study. The control group comprised 40 males and 6 females, while the case group comprised 13 males and 31 females (overall male:female ratio 1.45:1).

Baseline characteristics and iron profile

Table 1. Baseline demographic and anthropometric characteristics of cases and controls (Mean ± SD)

Parameter	Cases (n=44)	Controls (n=44)	p-value
Age (years)	33 ± 7.4	32 ± 7.5	0.561
Height (m)	1.657 ± 0.186	1.620 ± 0.091	0.239
Weight (kg)	59.568 ± 6.308	60.602 ± 10.282	0.568
BMI (kg/m²)	21.715 ± 2.135	22.966 ± 2.549	0.015*

Age, height and weight were comparable between groups; BMI was significantly lower in cases than controls (p = 0.015).

Table 2. Comparison of haematological indices and iron profile between cases and controls (Mean ± SD)

Parameter	Cases (n=44)	Controls (n=44)	p-value
Haemoglobin (g/dl)	7.246 ± 1.468	13.800 ± 1.295	<0.0001*
Haematocrit (%)	24.674 ± 4.216	41.838 ± 4.169	<0.0001*
MCV (fL)	65.188 ± 9.728	89.125 ± 6.545	<0.0001*
MCH (pg)	18.710 ± 3.647	28.387 ± 2.175	<0.0001*
MCHC (g/dl)	27.255 ± 3.025	34.516 ± 3.768	<0.0001*
Serum iron (µg/dl)	22.685 ± 12.445	100.339 ± 37.989	<0.0001*
TIBC (µg/dl)	472.839 ± 65.20	351.662 ± 59.56	<0.0001*
Serum ferritin (µg/l)	6.297 ± 3.869	86.502 ± 134.459	<0.0002*
Transferrin saturation (%)	6.052 ± 3.383	38.914 ± 11.106	<0.0001*

All haematological indices and iron-profile parameters were significantly reduced in cases compared with controls, confirming the biochemical diagnosis of iron deficiency anaemia, except TIBC, which was appropriately elevated in cases.

Optical coherence tomography findings

Table 3. Comparison of RNFL thickness (µm) between cases and controls, left eye

Quadrant	Cases (Mean ± SD)	Controls (Mean ± SD)	p-value
Superior	97.636 ± 22.718	125.717 ± 12.629	<0.0001*
Inferior	101.977 ± 23.856	136.196 ± 21.317	<0.0001*
Nasal	56.909 ± 9.889	87.413 ± 22.175	<0.0001*
Temporal	67.477 ± 13.755	91.196 ± 14.978	<0.0001*
Average	81.477 ± 14.153	109.326 ± 11.053	<0.0001*

Table 4. Comparison of RNFL thickness (µm) between cases and controls, right eye

Quadrant	Cases (Mean ± SD)	Controls (Mean ± SD)	p-value
Superior	103.977 ± 19.358	121.783 ± 27.235	<0.0001*
Inferior	107.409 ± 24.809	126.717 ± 26.725	<0.0001*
Nasal	67.750 ± 11.717	88.717 ± 13.530	<0.0001*
Temporal	57.295 ± 9.317	79.217 ± 17.779	<0.0001*
Average	84.045 ± 11.943	105.826 ± 13.086	<0.0001*

RNFL thickness was significantly reduced in all quadrants and in the average value, in both eyes, in cases compared with controls.

Table 5. Comparison of central macular thickness (CMT, µm) between cases and controls

Eye	Cases (Mean ± SD)	Controls (Mean ± SD)	p-value
Left eye	232.055 ± 9.622	269.500 ± 14.520	<0.0001*
Right eye	232.965 ± 9.263	269.199 ± 14.614	<0.0001*

Central macular thickness was significantly lower in cases than controls in both eyes.

Correlation of OCT with the anaemia/iron profile

Table 6. Correlation (Pearson's r) of OCT parameters with haemoglobin and iron profile, left eye

Parameter	Group	Superior	Inferior	Nasal	Temporal	Average	CMT
Hb	Control	0.125	-0.134	-0.414	-0.283	-0.313	0.398
	Cases	-0.043	-0.095	-0.134	-0.033	-0.126	0.029
S. Iron	Control	0.138	-0.090	-0.100	-0.120	-0.038	-0.110
	Cases	-0.007	0.037	0.064	-0.059	0.004	-0.095
TIBC	Control	0.043	0.071	0.153	0.242	0.137	0.224
	Cases	0.047	0.088	-0.140	-0.097	-0.003	0.030
S. Ferritin	Control	0.050	-0.082	-0.047	-0.081	-0.086	-0.161
	Cases	0.134	0.054	0.138	-0.052	0.092	-0.158
Trans. Sat.	Control	0.074	-0.065	-0.200	-0.184	-0.222	0.069
	Cases	0.334	0.149	0.147	0.087	0.258	-0.278

Table 7. Correlation (Pearson's r) of OCT parameters with haemoglobin and iron profile, right eye

Parameter	Group	Inferior	Nasal	Temporal	CMT
Hb	Control	0.124	0.201	0.149	0.462
	Cases	0.031	0.056	-0.033	0.083
S. Iron	Control	0.053	0.211	0.047	-0.030
	Cases	-0.067	0.055	-0.073	-0.110
TIBC	Control	0.053	-0.030	-0.053	0.163
	Cases	0.014	0.047	0.088	-0.140
S. Ferritin	Control	0.124	0.197	0.149	-0.061
	Cases	-0.164	0.134	0.054	0.138
Trans. Sat.	Control	-0.145	-0.096	-0.073	-0.030
	Cases	-0.002	-0.003	-0.070	-0.308

$r < 0.3$ = mild correlation; 0.3–0.5 = moderate correlation; $r > 0.5$ = strong correlation. Positive values indicate a positive correlation, negative values a negative correlation.

A moderate positive correlation was observed between haemoglobin and CMT in controls, and between transferrin saturation and CMT in cases, in the right eye. In the left eye, a moderate negative correlation was seen between haemoglobin and nasal RNFL thickness, and between haemoglobin and CMT, in controls. Correlations between OCT parameters and other iron-profile indices were mild, with both positive and negative associations seen in the two eyes.

DISCUSSION

The present study demonstrates significant structural abnormalities on OCT reduced RNFL thickness in all quadrants and reduced central macular thickness in adult patients of IDA compared with age- and sex-matched healthy controls.

Haematological and iron-profile findings

All haematological indices and iron-profile parameters were significantly reduced in cases compared with controls, confirming the diagnosis of IDA and consistent with previous reports by Akdogan et al.[16] and Cikmazkara et al.,[15] who also documented significantly lower haemoglobin and iron-profile values in IDA patients than controls.

RNFL and macular thickness findings

Mean RNFL thickness in all quadrants and the average value, in both eyes, were significantly thinner in IDA patients than controls, as was central macular thickness. It is well established that iron performs important functions in the CNS, including nerve myelination and neurotransmitter synthesis, and that oligodendrocytes crucial for myelination are adversely affected by iron deficiency.[9,10] These findings are consistent with Koca et al.[17] (2022), who reported significantly decreased mean RNFL thickness across superior, inferior, nasal and temporal quadrants and the average value in IDA subjects

compared with age- and sex-matched controls, and with Cikmazkara et al.,[15] who found thinner average RNFL in anaemic subjects than controls, reaching statistical significance in all quadrants except the superior quadrant.

Basset et al.[18] similarly found decreased peripapillary RNFL thickness in children with IDA, with significant thinning in inferior, superior and temporal quadrants. El-Gamal et al.[19] reported a positive association between average, nasal and inferior RNFL thickness and haemoglobin concentration in both eyes, with the degree of thinning related to the severity of anaemia. Samant et al.[20] (2022) similarly reported significant peripapillary RNFL thinning in adult IDA patients.

Reduced choroidal thickness has also been reported in IDA by Yumusak et al.[21] in reproductive-aged women and by Moussa et al.[22] in adult females and it has been suggested that OCT may have considerable value in the assessment of glaucoma, neuro-ophthalmological disorders and early IDA. Simsek et al.[23] reported significant RNFL thinning across all quadrants in children with IDA, and Jaiswal et al.[24] found similar RNFL thinning in adult IDA patients, both consistent with the present findings.

The mean central macular thickness in both eyes was significantly lower in case subjects than controls. Iron affects myelin synthesis both directly, as a cofactor of cholesterol and lipid biosynthesis, and indirectly, as a component of oxidative metabolism in oligodendrocytes; demyelination of nerve fibres results in decreased RNFL thickness.[9] Retinal dopaminergic dysfunction associated with iron deficiency is thought to alter the receptive area of axons and ganglion cells that constitute the RNFL.[11],[12]

Correlation of OCT with the anaemia profile

Correlation coefficients between OCT parameters and the anaemia/iron profile in the present study were largely mild, with occasional moderate correlations (e.g., haemoglobin with CMT, and haemoglobin with nasal RNFL, in controls). Vasospasm, venous stasis and hypoxia have been proposed as important contributors to the formation of anaemic retinal nerve fibre and choroidal disorders, and retinal ganglion cell and nerve fibre layer development may be affected in patients with IDA through these mechanisms in addition to direct iron-dependent effects on myelination.

CONCLUSION

Adult patients with newly diagnosed iron deficiency anaemia (Hb < 10.9 g/dl) show significant thinning of RNFL across all quadrants and of central macular thickness, in both eyes, compared with healthy controls. These structural changes indicate subclinical involvement of the retina and optic nerve in adult IDA. OCT is a non-invasive, objective and reproducible imaging tool that can be used for early detection and monitoring of ocular changes in patients of iron deficiency anaemia, and may have a role in assessing response to iron replacement therapy.

Limitations

- The sample size, though adequate as per a priori calculation, was relatively small; a larger cohort would strengthen the reliability of the findings.
- This was a case–control study; a longitudinal cohort design would provide stronger evidence of causality.
- A prospective pre- and post-treatment design in the same patients would better establish whether OCT changes are reversible with iron supplementation.

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