ORIGINAL ARTICLE

Evaluation of Macular and Peripapillary Capillary Density in Patients with Iron Deficiency Anemia

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Abstract

Background: ***According to World Health Organisation, 40% of infants aged 6 to 59 months , 30% of females aged 15 to 49 were anaemic. Iron deficiency is the leading cause of anaemia., the pathophysiology of fundus lesions in anemia is believed to be potentially linked to hypoxia.***

Aim: ***To study macular and peri-papillary microvascular changes in cases with iron deficiency anemia using optical coherence tomography angiography (OCT-A).***

Patients and Methods: ***A prospective cross-sectional study was conducted at Al-Zahraa University Hospital (Cairo, Egypt) with thirty IDA cases (group A, sixty eyes) , thirty healthy controls (group B, sixty eyes). OCT-A was used to measure vessel densities (VD) of macula, optic nerve head, foveal avascular zone (FAZ) in all subjects.***

Results: ***Mean age was 33.93±9.35 in group A, 32.63±4.00 in group B (P=0.073). Women made up 86.7percent of both groups. Tested groups showed statistically significant differences in average GCC (P=0.046), superior GCC (P=0.036), superior RNFL (P<0.001), and inferior RNFL (P<0.001). In comparison to the control group, the IDA group had considerably lower macular vascular density in all macular regions in both SCP and DCP (P<0.003). RPCvd was significantly lower in the area inside the disc (P<0.001) but not in the entire image or the peripapillary area (P>0.05). There was no statistically significant difference between the 2 groups in the FAZ area. In both SCP (sup hemifield, perifovea) and DCP (perifovea).***

Conclusion: ***In IDA cases, both macular and peripapillary vascular density were diminished. OCT-A can be beneficial in detecting retinal ischaemia before clinically apparent retinopathy caused by IDA.***

Keywords: Iron deficiency anaemia; OCT-A, macula; optic disc; vessel density

1. Introduction

Anaemia is known as having a low red blood cell count, haematocrit, or haemoglobin concentration .[1] Anaemia reduces capacity to transport oxygen .[2]

WHO estimates showed 40 percent of toddlers aged 6 to 59 months, 37 percent of pregnant women, and 30 percent of women aged fifteen to forty-nine years were anaemic worldwide. While there were different kinds of anaemia, IDA was the most common. IDA affects four-five million people per year .[3]

Iron was abundant in haemoglobin (Hb), which transports oxygenated blood to all organs.[4] It plays an essential function in central nervous system, including proper myelination, neurotransmitter production, neurometabolism.[5]

Because the vascular system was incapable of transporting adequate oxygen throughout the body, hypoxia was unavoidable in IDA .[3] Hypoxia has been linked to negative outcomes in a variety of bodily systems, including the eye (2). Iron was required for oxygen transport, and the pathogenesis of fundus lesions in anaemia was thought to be associated with hypoxia .[5] In retinal tissue, photoreceptor cells rely on iron-containing enzymes to synthesise lipids required to form new disc membranes .[6] Iron deficiency has been linked to a reduction in visual evoked potential. Low oxygen flow has been proven to induce injury to the ganglion.[7]

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OCT-A was a non-invasive light-based imaging technology that identifies movement in retinal blood vessels by evaluating the difference in reflected OCT signal amplitude between consecutive cross-sectional scans.[8] OCT-A detects high-resolution blood flow in various levels of the retina and provides 3-dimensional images of these vascular layers. This capability allows quantitative measurements of microvascular architecture and blood flow in capillaries .[5]

There was a dispute between earlier studies. Some studies observed thinner peripapillary RNFL thickness measured by OCT in adult females with IDA [9], while others reported lower peripapillary capillary vessel density values in IDA compared to the control group with no significant variations in RNFL thickness values .[2] A recent study demonstrated drastically low macular vascular density in all macular regions, except the fovea. Decrease in vessel density of the optic disc in the IDA group without RNFL thinning .[10] In the present study, we aim to study macular, peri-papillary microvascular changes in cases with iron

2. Patients and methods

This prospective cross-sectional study was conducted at Al-Zahraa University Hospital in Cairo, Egypt, from May 2023 to June 2024, and included thirty cases with IDA, thirty healthy participants (Group B) aged twenty to forty-five. The Study protocol was approved by Al-Azhar University's Local Ethics Committee (No: 1839), and each subject provided informed written consent to participate in the study. The Study protocol followed the precepts of the Declaration of Helsinki. Confidentiality and personal privacy were respected at all levels of study.

ases with a history of ocular disease, such as glaucoma, uveitis, Prior ocular surgery, Systemic or chronic disease (as Diabetes mellitus (DM), kidney or liver disease), Pregnant women, and errors of refraction more than 4 diopters sphere and /or 3 diopters cylinder, were excluded from the study.

Laboratory findings for IDA include serum Hb levels of <thirteen g/dl in males, < twelve g/dl in females, MCV of <eighty fL, MCH of < twenty-three pg/erythrocyte, serum transferrin saturation (TSATpercent) of < fifteen percent, serum iron (ug/dL), and TIBC (ug/dl).

OCT-A measurements: XR Avanti OCT-A was performed using AngioVue (RTVue XR AVANTI, Optovue, Fremont, CA, USA) to capture six mm × six mm macular images centred on the foveola. Additionally, each patient had 4.5 × 4.5 mm optic disc pictures taken. The Thickness of the RNFL and the macular ganglion cell complex (GCC) was assessed. Images with a quality score of <six were repeated until they were of good quality, otherwise excluded.

In all cases, A sequence of B-scans was used to perform a GCC scan, with the fovea centred 1 millimetre temporally. GCC protocol consisted of fifteen vertical lines with a scanning length of seven mm, separated by a 0.5 mm spacing, and 1 horizontal line with a scanning length of seven mm. After evaluating scans, the gadget calculated GCC thickness, which was defined as the distance between the internal limiting membrane (ILM) and the outside boundary of the inner plexiform layer (IPL). RTVue XR Avanti device measures GCC individually for superior and inferior eye sectors, yielding three different values: superior sector GCC thickness (sup. GCC), inferior sector GCC thickness (inf. GCC), and average thickness of both sectors (avg. GCC).

A rapid RNFL thickness procedure was used using OCT to scan the RNFL at the peripapillary level. RNFL thickness metrics used for evaluation were ordinary, inferior, superior RNFL thickness.

Macular scanning measured vessel density (VD), foveal avascular zone (FAZ), and macular flow area. Macular scanning pictures of six mm × six mm were centred on the foveola. The macula was separated into 3 concentric rings of one-, three-, and six-mm width, referred to as fovea, parafovea, and perifovea. Device software automatically separates all rings into 2 hemifields (superior & inferior), four quadrants (temporal, superior, nasal, inferior).

Scan optic discs with 4.5 × 4.5 mm fields. gadget used 2 ONH-centered concentric circles with dimensions of 2 mm (inner) , four mm (outer) to determine radial peripapillary capillary (RPC) vd (percent).

Statistical methods: Data were coded and entered into SPSS version twenty-eight (IBM Corp., Armonk, NY, USA). Quantitative data were summarised using mean, standard deviation, median, minimum, and maximum, whilst categorical data were summarised using frequency (count) and relative frequency (percentage). Unpaired t tests were employed to compare groups in normally distributed quantitative variables, while non-normally distributed quantitative variables were compared with the non-parametric Mann-Whitney test (Chan, 2003a). A chi-square (c2) test was employed to compare categorical data. When the expected frequency was less than 5, Chan (2003b) used an exact test instead. Quantitative variables were compared using the Spearman correlation coefficient (Chan, 2003c). P-values less than 0.05 were considered statistically significant.

3. Results

This prospective cross-sectional study included sixty eyes of thirty cases with IDA (group A), sixty eyes of thirty healthy subjects (group B). There were four (13.3percent) men , twenty six (86.7percent) women in both groups , mean age was 33.93±9.35 years in group A , 32.63±4.00 years in control group, with no significant differences between studied groups (p = 0.073), table (1).

Table 1. Baseline demographic characteristics; Comparison between 2 study groups

VARIABLES		GROUP A (TOTAL=30)	GROUP B (TOTAL=30)	P-VALUE
AGE (YEARS)	Mean ± SD	33.93±9.35	32.63±4.00	0.073*
GENDER	man	4 (13.3%)	4 (13.3%)	1.0**
	woman	26 (86.7%)	26 (86.7%)	

Upon fundus examination, none of our cases showed clinically evident indications of IDA retinopathy. mean Hb, MCV, MCH, RDW, Tsat percent, TIBC, UBIC values in group A were substantially different from those in control group.Table (2).

Table 2. Hematological parameters; Comparison between 2 study groups

	A (TOTAL=THIRTY)		B (TOTAL=THIRY)		P-VALUE (INDEPENDENT T-TEST)
	Mean	SD	Mean	SD	
HB	6.95	1.59	11.61	0.74	< 0.001
MCH	29.80	22.53	26.67	1.56	0.003
MCV	54.82	19.66	83.56	1.95	< 0.001
RDW	18.66	3.95	10.37	1.10	< 0.001
SERUM IRON	19.52	13.43	89.03	11.98	< 0.001
TSAT %	4.91	3.56	25.97	4.06	< 0.001
TIBC	409.87	72.40	346.37	39.15	< 0.001
UIBC	375.03	90.09	185.80	18.13	< 0.001

Table 4 shows RNFL and GCC thickness. Although RNFL and GCC thickness were lower in group A, difference was not statistically significant in Inferior GCC or Average RNFL. In group A, average GCC , superior GCC were significantly decreased compared to control group (p = 0.046, p = 0.036, respectively). superior RNFL , inferior RNFL were significantly decreased compared to control group (p <0.001).

Table 3. OCT parameters GCC, RNFL; Comparison between 2 study groups

	GROUP A (TOTAL=60)		GROUP B (TOTAL=60)		P-VALUE (INDEPENDENT T-TEST)
	Mean	SD	Mean	SD	
AVERAGE GCC	97.82	9.62	101.30	9.32	0.046
SUPERIOR GCC	97.60	9.25	102.03	13.27	0.036
INFERIOR GCC	97.83	10.40	100.47	6.93	0.105
AVERAGE RNFL	102.83	11.75	101.82	7.16	0.568
SUPERIOR RNFL	105.05	13.60	121.10	14.67	< 0.001
INFERIOR RNFL	100.35	13.00	119.87	14.82	< 0.001

Group A showed significantly lower mean vessel density in SCP , DCP compared to control group (p < 0.001). Table (5) shows that peripapillary RPC vessel density decreased considerably in interior disc (p < 0.001) but not in overall image or peripapillary area (p = 0.595, p = 0.972).

Table 4. OCT A parameters; Comparison between the two study groups

	A (TOTAL=SIXTY)		B (TOTAL= SIXTY)		P-(INDEPENDENT T-TEST)
	Mean	SD	Mean	SD	
VESSEL DENSITY, SCP FLOW (%)					
WHOLE RETINA	47.00	3.32	49.49	3.37	< 0.001
SUP HEMI	47.22	3.60	49.67	3.21	< 0.001
INF HEMI	46.78	3.72	50.45	7.34	< 0.001
FOVEA	18.00	7.97	21.83	5.52	0.003
PARAFOVEA	48.86	3.96	52.25	3.73	< 0.001
PERIFOVEA	48.04	3.81	50.25	3.37	< 0.001
VESSEL DENSITY, DCP FLOW (%)					
WHOLE RETINA	44.65	5.79	49.89	5.44	< 0.001
SUP HEMI	44.62	7.58	50.46	5.10	< 0.001
INF HEMI	44.06	7.35	48.99	7.97	< 0.001
FOVEA	34.03	8.97	38.90	6.62	< 0.001
PARAFOVEA	51.84	7.14	55.46	3.75	< 0.001
PERIFOVEA	45.91	6.53	51.62	5.43	< 0.001
RADIAL PERIPAPILLARY CAPILLARY (RPC) DENSITY, OPTIC DISC					
WHOLE	49.74	3.40	50.02	2.15	0.595
INSIDE DIS	46.97	6.15	51.22	5.37	< 0.001
PERIPAPILLARY	52.11	4.19	52.13	2.87	0.972
FAZ AREA (MM^2)	0.31	0.13	0.27	0.08	0.053

In correlation analysis, there was a significant positive correlation between serum Hb percent , vessel density of SCP (sup. hemifield, p = 0.006 , perifovea, p = 0.034), between serum Hb percent , vessel density of DCP (perifovea, p = 0.034). There was a significant negative correlation between serum iron , RNFL thickness (inferior, r=-0.278, p = 0.031). There was a significant negative correlation between Transferrin saturation , RNFL thickness (average NFL, r=-0.301, p = 0.019 , inferior NFL r=-0.337, p = 0.008), between Transferrin saturation , vessel density of SCP (fovea, p=0.034). correlation between mean corpuscular volume, total iron binding capacity , OCT, OCT-A parameters were non-significant, (table 6).

Table 5. Correlation analyses between capillary density , other parameters in study group (Group A)

	MCV		HB		SERUM IRON		TSAT %		TIBC	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
AVERAGE GCC	0.143	0.275	0.054	0.684	-0.089	0.497	-0.123	0.349	-0.086	0.514
SUPERIOR GCC	0.150	0.251	0.026	0.843	-0.063	0.634	-0.094	0.477	-0.106	0.419
INFERIOR GCC	0.140	0.287	0.073	0.577	-0.101	0.441	-0.132	0.315	-0.104	0.427
AVERAGE RNFL	0.113	0.390	0.013	0.919	-0.203	0.119	-0.301	0.019	-0.023	0.859
SUPERIOR RNFL	0.221	0.089	-0.040	0.759	-0.046	0.730	-0.157	0.231	-0.013	0.924
INFERIOR RNFL	0.016	0.904	0.025	0.847	-0.278	0.031	-0.337	0.008	-0.028	0.835
VD (SCP)- WHOLE RETINA	-0.024	0.855	0.252	0.052	-0.038	0.771	-0.052	0.693	0.159	0.226
VD (SCP)-SUP HEMI	0.024	0.858	0.353	0.006	0.136	0.300	0.090	0.495	0.206	0.114
VD (SCP)- INF HEMI	-0.055	0.677	0.136	0.301	-0.159	0.226	-0.152	0.245	0.106	0.421
VD (SCP)- FOVEA	0.054	0.681	-0.171	0.192	-0.245	0.060	-0.274	0.034	0.203	0.120
VD (SCP)- PARAFOVEA	0.015	0.911	0.212	0.103	0.039	0.767	0.013	0.920	0.069	0.598
VD (SCP)- PERIFOVEA	-0.009	0.946	0.274	0.034	0.067	0.610	0.037	0.781	0.144	0.274
VD (DCP)- WHOLE RETINA	0.126	0.336	0.218	0.095	0.047	0.724	0.081	0.537	0.149	0.255
VD (DCP)- SUP HEMI	0.112	0.396	0.169	0.196	0.125	0.343	0.136	0.299	0.078	0.554

VD (DCP)- INF HEMI	0.072	0.582	0.154	0.239	0.010	0.939	0.053	0.687	0.105	0.426
VD (DCP)- FOVEA	0.059	0.656	-0.199	0.127	-0.168	0.201	-0.200	0.125	0.108	0.413
VD (DCP)- PARAFOVEA	0.077	0.561	0.105	0.425	0.095	0.469	0.124	0.344	0.087	0.510
VD (DCP)- PERIFOVEA	0.083	0.527	0.274	0.034	0.068	0.607	0.100	0.449	0.128	0.330
VD (OD) -WHOLE DISC	0.010	0.939	0.110	0.403	0.058	0.661	0.103	0.435	-0.067	0.610
VD (OD) -INSIDE DIS	0.102	0.437	0.034	0.796	0.121	0.357	0.183	0.163	-0.238	0.067
VD (OD) - PERIPAPILLARY	-0.023	0.859	0.121	0.356	0.026	0.846	0.055	0.674	-0.003	0.984

4. Discussion

We employed OCTA to analyse microvascular alterations in the retina andthe optic nerve head in IDA cases. study included thirty IDA cases (Group A) , thirty age-matched healthy control subjects (Group B).

The research group included twenty-six (86.7 percent) women and four (13.3 percent) men, while the control group had twenty-six (86.7 percent) women and four (13.3 percent) men. According to Zopfs et al.[11], anaemia was a widely prevalent condition with a global prevalence of up to 24.8percent, with females being more affected than males. According to the World Health Organisation (WHO), rates were 12.7 percent, 30.2 percent, and 41.8 percent for adult males, females of reproductive age, and pregnant females, respectively[12]. Similar to our study, Koca et al.[10] enrolled twenty-nine women and four men with IDA in the same control group. Kocer et al.[2] included thirty-five women & five men with IDA & thirty-seven women, nine men in the control group.

In the current study, we discovered that peripapillary RNFL was thinner in cases with IDA ($P< 0.001$ for both superior and inferior peripapillary RNFL, although average RNFL thicknesses were equal in A and B ($p=0.568$). In a study of seventy-three eyes with IDA, sixty-eight healthy controls with mild to moderate anaemia, Acir et al.[13] discovered that cases with IDA had significantly decreased peripapillary RNFL in the nasal inferior quadrant. IDA, control groups had identical average RNFL thicknesses (84.4 ± 5.9, 85.3 ± 4.5).In a study by Cikmazkara, Ugurlu (9), 102 women with IDA were compared to forty-nine age, sex-matched controls. The IDA group exhibited lower average RNFL thickness ($P = 0.001$). The IDA group had thinner average RNFL thicknesses in the temporal, nasal, and lower quadrants compared to the control group ($P = 0.001$, $P = 0.013$, $P = 0.008$, respectively). Two additional earlier studies evaluated RNFL thickness in cases with IDA, revealing a substantial drop in average RNFL thickness in all four quadrants in IDA cases compared to the control group.

In contrast, Koca et al.[10] reported that RNFL thickness was lower in IDA group in peripapillary region , all four quadrants, but difference was not statistically significant. In their investigation, average Hb level was 8.7 g/dL, which was higher than in our cases. Kocer et al.[2] reported that subjects with IDA (40 cases) , control group (46 healthy volunteers) had similar RNFL thickness.

In our investigation, we discovered that Macular GCC was thinner in A than in B, with a significant difference in average, superior GCCs ($P= 0.046$, $P=0.036$, respectively). Acir et al.[13]

Both SCP and DCP macular vascular density assessments showed a significant reduction in all macular regions among IDA cases ($P < 0.003$). Similarly to our study, Koca et al.[10] found a significant drop in SCP and DCP macular vascular density analysis in IDA participants, with the exception of the fovea.

Korkmaz et al.[5] revealed a considerable decrease in vessel density over SCP. They discovered that the difference in DCP was not substantial (except for the inferior parafovea and the temporal perifovea). Düzgün et al.[15] discovered that, while macular vascular density of SCP decreased significantly in all parafoveal quadrants across the retina, there was no statistically significant change in DCP vessel density in any parafoveal quadrant. While our study's mean Hb level was 6.95 g/dL, Korkmaz et al.[5] and Düzgün et al.[15] discovered 10.3 g/dL and 9.4 g/dL, respectively. Lower mean Hb levels and more severe anaemia in our study may explain a more significant loss in vascular density.

In our study, A had a larger FAZ area, although difference was not statistically significant ($P=0.053$). Similarly to us, Koca et al.[10] found no statistically significant variations in FAZ between 2 groups. According to Korkmaz et al.[5], mean FAZ value was 0.290 ± 0.09 mm2 in study group , 0.298 ± 0.11 mm2 in control group.

Düzgün et al.[15] found that the mean foveal avascular zone area was considerably reduced in the IDA group ($p < 0.05$).

We discovered a favourable relationship between RNFL thickness (mean, superior, inferior) and MCV, serum Hb percent. A negative relationship was identified between iron, Tsat, TIBC, and RNFL thickness measures. Similarly, Cikmazkara & Ugurlu[9] discovered a positive link between mean RNFL thickness, serum Hb percent, iron, ferritin, transferrin saturations, but a negative correlation between total iron binding capacity and mean RNFL thickness. Datta et al.[16] discovered a positive relationship between average RNFL thickness, serum haemoglobin, iron, ferritin, and transferrin levels (P value = 0.02). Similarly, Joshi, Ingle[7], Gupta et al.[14] discovered a favourable relationship between average RNFL thickness, serum Hb percent, iron, and ferritin. On the contrary, Akdogan et al.[17] found no relation to any blood markers.

We discovered a favourable relationship between GCC thickness (mean, superior, inferior), both MCV, and serum Hb percent. A negative relationship was identified between iron, Tsat, TIBC, and RNFL thickness measures. Acir et al. [13] discovered that measurements of macula GCL+ thicknesses were comparable between groups (seventy-three eyes of thirty-nine cases with ID anaemia, sixty-eight eyes of thirty-four sex-matched healthy volunteers), but no link was identified between these parameters.

In our investigation, there was a strong positive connection between serum Hb percent, SCP vessel density (sup hemifield, perifovea), and DCP vessel density (perifovea). Düzgün et al.[15] identified a positive relationship between whole-parafoveal vascular density of SCP, haematological markers, including Hb, Hct, MCV, and MCH ($p < 0.01$), similar to our findings. Children with IDA showed similar results to those in our study. Korkmaz et al. found that SCP had a greater reduction in perifoveal vascular density than DCP in children with IDA. This difference can be attributable to differences in physiologic age .[18]

We discovered a positive link between RPCvd values , haematological measures ex MCV, Hb percent, iron, Tsat.percent, as well as a negative correlation between TIBC , RPCvd values, none of these relationships were significant.

On the other hand, Kocer et al.[2] discovered multiple substantial positive correlations between RPCvd values, haematological markers, such as Hb, HCT, MCV, MCH, MCHC, and ferritin.

4. *Conclusion*

In IDA cases, both macular and peripapillary vascular density were reduced. OCT-A can be beneficial in detecting retinal ischaemia before clinically apparent retinopathy caused by IDA. Mean Hb level may be a predictor of reduced macular and optic disc vascular density.

Disclosure

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