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Evaluation of macular and optic disc radial peripapillary vessel density with optical coherence tomography angiography in iron deficiency anemia

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ABSTRACT

Purpose: To investigate effect of iron deficiency anemia (IDA) on macular and radial peripapillary capillary (RPC) vascular changes by optical coherence tomography angiography (OCTA).
Methods: Thirty-three patients with IDA and 33 healthy controls were enrolled in the study. Foveal avascular zone (FAZ) area, macular superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel density and RPC vessel density were evaluated by the AngioVue Imaging System. Hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), serum iron, total iron-binding capacity (TIBC), serum ferritin and transferrin saturation values were also recorded.
Results: There were no statistically significant differences between the two groups in terms of FAZ area and FAZ perimeter while foveal density (FD) was significantly decreased in the IDA group. Compared to control group, IDA group revealed significantly decreased macular vessel density in all macular regions except fovea in both SCP and DCP. RPC vessel density was significantly decreased in whole image, peripapillary and superior-hemifield area wihout RNFL thinning. Hemoglobin level was positively correlated with SCP whole and RPC whole vessel density and serum iron level was also positively correlated with SCP whole vessel density.
Conclusion: Macular and optic disc vessel density were reduced in IDA patients. OCTA may be useful in detecting retinal ischemia before clinically visible signs of retinopathy associated with IDA appear.

1. Introduction

Iron deficiency anemia (IDA) is the most common cause of anemia and affects >1.2 billions individuals globally [1]. IDA is caused by decreased dietary intake, increased iron requirements especially in children, adolescents and pregnants, repeated blood loss and digestive malabsorption of iron. Anemia leads to clinical and functional impairments in many organs and systems. In IDA, hemoglobin (Hb) concentration is low and oxygen transport capacity to tissues is reduced. The retina and choroid are one of the most metabolically active tissues in the body and consume high level of nutrients and oxygen to maintain their visual function. Therefore these tissues have dense and complex vascular network. Retinochoroidal circulation may be disturbed in patients with abnormalities of blood components such as IDA [2]. Iron is an essential element for myelination and neurotransmitter signaling of optic disc. An animal study concluded that iron is necessary for maintenance of the optic nerve cell structure [3].

Optical coherence tomography angiography (OCTA) is a non-invasive light-based imaging device that can detect motion in blood vessel lumen by measuring the variation in reflected OCT signal amplitude between consecutive cross-sectional scans [4]. The ability of OCTA to visualize the high resolution microvascular structure seperately has allowed us to explore foveal avascular zone (FAZ) area, macular deep and superficial capillary plexus and radial peripapillary capillary (RPC) network.

In this study we aimed to evaluate macular and RPC vascular changes in IDA with OCTA. Additionnaly, we investigated the relationship between retinal vascular parameters and hematological parameters.

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2. Materials and methods

2.1. Study population

This single-centered prospective comparative study was performed in the Department of Ophthalmology and Internal Medicine Clinic of Afyonkarahisar Health Sciences University. The study protocol was approved by the Ethics Committee of the Afyonkarahisar Health Sciences University, and the study was conducted in accordance with the ethical principles of the Helsinki Declaration. Informed written consent was obtained from all the participants.

Hemoglobin (Hb) (g/dL), hematocrit (Hct) (%), MCV (fL), mean corpuscular hemoglobin (MCH) (pg), red cell distribution width (RDW) (%) values were indicated in both groups. Additionally in IDA group, serum iron (ug/dL), total iron-binding capacity (TIBC) (ug/dl), serum ferritin (ng/mL) and transferrin saturation (%) levels were implied. IDA diagnosis was based on the Hb level less than 13.5 g/dL for males, 12.0 g/dL for females, ferritin level <30 ng/mL (normal 20–300 ng/mL), transferrin saturation lower than 20%, and MCV less than 80 fL [5]. In cases with IDA, further investigations were made for the etiology and only the cases due to dietary insufficiency of iron were included in the study.

The control group consisted of healthy volunteers similar in terms of demographic characteristics. For both groups the exclusion criteria were spherical or cylindirical refractive error greater than ±2 diopters, uveitis, intraocular pressure greater than 20 mmHg or glaucomatous optic neuropathy, optic nerve or retinal diseases, history of ocular surgery or trauma, significant media opasity and cataract that may affect posterior segment examination and OCTA measurements, presence of pregnancy, defined systemic or chronic disease previously.

2.2. Study protocol

Each subject underwent a comprehensive ophthalmic examination including best corrected visual acuity, intraocular pressure masuremets with non-contact tonometry, anterior and dilated fundus examination and OCTA. Only the right eye of each participants was used for analysis.

OCTA measurements were obtained by the AngioVue Imaging System (RTVue XR Avanti; Optovue, Inc. Fremont, CA) using split-spectrum amplitude-decorrelation angiography (SSADA) algorithm to reduce scanning time. The system has an A scan rate of 70,000 scans per second using a light source centered on 840 nm and a bandwidth of 45 nm [4]. In addition to the assessment of the retinal microvascular structure, device allows us to provide quantitative data such as flow and non-flow area, foveal avascular zone (FAZ) and vessel density (VD). All measurements were made by the same experienced examiner after pupil dilatation and images with poor quality (lesser than 7/10) or motion artifacts excluded from the study. An independent researcher evaluated the images in terms of accurate segmentation and image quality. Manual segmentation was performed on eyes where automatic segmentation was not accurate.

FAZ area was measured as mm^2 automatically in whole retina. Perimeter (PERIM, mm) and foveal density (FD, %) were also evaluated. For macular evaluation 6 × 6 mm scan size centered on the macula was used. Macula was divided into 1, 3 and 6 mm width 3 concentric rings and these rings were defined as fovea, parafovea and perifovea, respectively. All rings are seperated into two hemi-field (superior and inferior) and four quadrants (temporal, superior, nasal and inferior) by device software automaticcally. Superficial capillary plexus (SCP) was defined as the region between the internal limiting membrane to 9 μm below the inner plexiform layer. Deep capillary plexus (DCP) was bordered between 9 μm below the inner plexiform layer and 9 μm above the outer plexiform layer. In both SCP and DCP automatic segmentation was used for VD which is the percentage area occupied by flowing blood vessels in selected region.

Optic disc measurements were obtained by 4.5 × 4.5 mm optic disc scans centered on optic disc circumferentially. The borders were defined as internal limiting membrane to retinal nerve fiber layer (RNFL) posterior boundary. Small vessel RPC density in whole image, inside disc and peripapillary area and all four quadrants (superior, temporal, inferior and nasal) were noted. Peripapillary and four quadrants (superior, temporal, inferior and nasal) RNFL thickness obtained by OCTA were also measured.

2.3. Statistical analysis

In statistical analysis, mean, standard deviation, minimum and maximum values of numerical data were calculated. Categorical data were expressed as frequency and percentage (%). Shapiro Wilk test was used to evaluate normality assumption. Furthermore, data with kurtosis and skewness values in the range of -1.5, +1.5 were accepted as the demonstration of normal distribution. Levene test was used to evaluate the homogeneity of variances. Student's *T* test was utilized to evaluate the difference in terms of mean values between the groups when the parametric test assumptions were provided, and the Mann Whitney U test was used if the parametric test assumptions were not met. In order to show the relationship between the groups, Pearson correlation analysis was used in the groups with normal distribution, and Spearman correlation analysis was used if they did not show normal distribution. Statistically, a p value of <0.05 was considered significant. SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) software program was used for all analyzes.

3. Results

The study involved a total of 33 eyes of 33 IDA patients and a total of 33 eyes of 33 sex matched controls. There were 4 (12.1%) males and 29 (87.9%) females in both groups and the mean age was 42.7 ± 9.3 years (range, 22-71 years) in IDA group and 42.9 ± 9.4 years (range, 24–71 years) in the control group. There was no statistically significant difference between groups in terms of age ($p = 0.99$). On dilated fundus examination none of the patients had clinically visible signs of IDA retinopathy. Hematologic parameters were summarized in Table 1. Compared to control group, the mean Hb, Hct, MCV, MCH and RDW values were significantly different in IDA group. Also in IDA group, transferrin saturation was 5.7 ± 4.5 % (2.9- 26.1) and TIBC was 362.9±117.1 ug/dL (102-511). Serum iron and ferritin level were 21.4 ± 14.2 ug/dL (12–93) and 5.0 ± 3.3 ng/mL (1.3–13.5), respectively.

The mean values of FAZ area, PERIM, FD and SCP vascular density were shown in Table 2. While there were statistically no significant differences between the groups with regard to FAZ area ($p = 0.42$) and FAZ PERIM ($p = 0.59$), FD ($p = 0.003$) was significantly lower in IDA group compared to control group. In IDA group, a significant decreased SCP vessel density was found in all macular areas except fovea.

Comparison and mean values of vessel density in DCP are given in Table 3. At the DCP, IDA patients revealed a significantly decreased vessel density compared to control subjects in all macular regions except fovea.

Table 4 shows optic disc analysis including RNFL thickness and RPC vessel density. Although RNFL thickness was lower in IDA group in

Table 1
Comparison of hematologic parameters between groups.

	IDA group	Control group	p
Hb (g/dL)	8.7 ± 2.0	13.4 ± 0.5	0.000
Hct (%)	30.3 ± 4.7	40.1 ± 3.1	0.000
MCV (fL)	70.8 ± 7.5	87.8 ± 2.3	0.000
MCH (pg)	20.1 ± 3.5	29.7 ± 1.7	0.000
RDW (%)	18.8 ± 2.5	12.2 ± 0.5	0.000

Hb: Hemoglobin, Hct: Hematocrit, IDA: Iron deficiency anemia, MCH: Mean corpuscular hemoglobin, MCV: Mean corpuscular volume, RDW: Red cell distribution width.

Table 2
Comparison of FAZ and SCP vessel density parameters.

	IDA Group	Control Group	p
FAZ area (mm^2)	0.289 ± 0.096	0.309 ± 0.101	0.42
FAZ Perimeter (mm^2)	2.085 ± 0.362	2.132 ± 0.369	0.59
FD (%)	53.3 ± 4.4	56.2 ± 2.9	0.003
Whole image	47.2 ± 2.9	52.6 ± 2.3	0.000
Superior-Hemi	47.0 ± 3.1	52.6 ± 2.1	0.000
Inferior- Hemi	47.4 ± 2.9	52.5 ± 2.6	0.000
Fovea	17.5 ± 5.9	19.8 ± 6.1	0.12
Parafovea	48.8 ± 4.2	55.0 ± 2.5	0.000
Superior-Hemi	49.5 ± 3.9	55.2 ± 2.8	0.000
Inferior- Hemi	48.2 ± 4.8	54.8 ± 2.6	0.000
Temporal	48.6 ± 4.2	54.4 ± 3.1	0.000*
	48.8 (46.8- 51.3)	55.4 (52.4- 56.7)	
Superior	50.2 ± 4.4	56.1 ± 3.4	0.000
Nasal	47.5 ± 5.4	53.9 ± 3.0	0.000*
	49 (45.9- 50.5)	54.3 (52.1- 55.4)	
Inferior	48.4 ± 4.7	55.4 ± 2.3	0.000*
	50.1 (45.6–51.5)	55.1 (53.8–56.3)	
Perifovea	47.6 ± 2.9	53.1 ± 2.3	0.000
Superior-Hemi	47.2 ± 3.4	53.1 ± 2.3	0.000
Inferior- Hemi	47.9 ± 2.9	53.0 ± 2.6	0.000
Temporal	44.2 ± 3.6	49.6 ± 2.5	0.000
Superior	47.4 ± 3.5	53.2 ± 2.5	0.000
Nasal	51.1 ± 2.9	56.3 ± 2.4	0.000
Inferior	47.9 ± 3.3	53.2 ± 3.0	0.000

FAZ: Foveal avascular zone, FD: Foveal density, IDA: Iron deficiency anemia, SCP: Superficial capillary plexus, * Mann Whitney U test was used to compare groups those not normally distributed.

Table 3
Comparison of DCP vessel density parameters.

	IDA Group	Control Group	p
Whole image	49.9 ± 7.7	55.3 ± 4.7	0.001
Superior-Hemi	49.7 ± 7.8	55.0 ± 4.6	0.002
Inferior- Hemi	50.2 ± 7.9	55.7 ± 5.1	0.001
Fovea	34.7 ± 8.8	37.0 ± 7.5	0.25
Parafovea	52.5 ± 6.2	58.1 ± 3.3	0.000
Superior-Hemi	53.9 ± 4.9	58.1 ± 3.1	0.000
Inferior- Hemi	52.8 ± 5.9	58.0 ± 3.6	0.000
Temporal	53.9 ± 5.0	58.8 ± 3.3	0.000
Superior	53.2 ± 5.9	57.7 ± 3.5	0.000
Nasal	54.0 ± 4.3	58.3 ± 3.7	0.000
Inferior	51.7 ± 7.2	57.4 ± 3.6	0.000
Perifovea	51.4 ± 8.2	56.8 ± 5.0	0.002
Superior-Hemi	51.5 ± 8.1	56.5 ± 5.0	0.004
Inferior- Hemi	51.4 ± 8.6	57.2 ± 5.4	0.002
Temporal	53.0 ± 6.7	58.4 ± 4.0	0.000
Superior	50.7 ± 8.7	55.6 ± 5.9	0.01
Nasal	51.3 ± 8.8	56.1 ± 5.4	0.003
Inferior	50.7 ± 9.4	57.3 ± 6.1	0.001

IDA: Iron deficiency anemia, DCP: Deep capillary plexus

peripapillary region and all four quadrants, the difference was not statistically significant. In IDA group, peripapillary RPC vessel density was significantly decreased in whole image, peripapillary and superior-hemifield area compared to control group ($p = 0.009$, $p = 0.03$ and $p = 0.02$, respectively). While peripapillary RPC vessel density was higher in inside disc, peripapillary inferior-hemifield and all four quadrants (superior, temporal, inferior, nasal) was lower than the control group, the difference was not statistically significant.

In the IDA group, the FAZ area and DCP whole vessel density was not correlated with none of the hematalogic parameters (Table 5). Hemoglobin level was positively correlated with SCP whole and RPC whole vessel denisty ($p = 0.04$ and $p = 0.04$, respectively) (Fig. 1). Positive significant association was also observed between serum iron level and SCP whole vessel density ($p = 0.03$) (Fig. 2).

Table 4
Comparison of optic disc parameters between groups.

RNFL thickness	IDA group	Control group	p
Peripapillary	116.1 ± 10.5	118.7 ± 11.7	0.42
Superior	135.4 ± 19.8	136.4 ± 15.4	0.82
Temporal	74.4 ± 10.5	78.0 ± 7.9	0.11
Inferior	147.6 ± 20.5	152.0 ± 18.0	0.34
Nasal	109.8 ± 17.8	106.4 ± 16.2	0.41
RPC density			
Whole image	48.0 ± 2.1	49.5 ± 2.2	0.009
Inside disc	51.9 ± 3.6	52.5 ± 3.8	0.53
Peripapillary	49.4 ± 2.9	51.1 ± 3.1	0.03
Superior-hemi	48.9 ± 3.3	50.9 ± 3.5	0.02
Inferior-hemi	49.7 ± 2.7	49.9 ± 8.5	0.08*
	48.9 (48.3–51.5)	50.9 (48.7–53.0)	
Superior	49.3 ± 3.3	50.4 ± 3.9	0.26
Temporal	52.7 ± 3.8	53.4 ± 3.9	0.54
Inferior	51.3 ± 3.0	52.7 ± 4.1	0.11
Nasal	47.4 ± 3.8	48.9 ± 3.3	0.07

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 group.

		FAZ area	SCP whole	DCP whole	RPC whole
Hemoglobin (g/dL)	r	-0.00	0.35	0.24	0.36
	p	0.96	0.04	0.17	0.04
Transferrin saturation (%)*	r	-0.16	0.32	0.22	-0.03
	p	0.35	0.06	0.22	0.83
TIBC (ug/dL)	r	0.34	-0.18	0.18	0.01
	p	0.06	0.32	0.32	0.92
Serum iron (ug/dL)*	r	-0.11	0.38	0.19	-0.01
	p	0.51	0.03	0.27	0.93
Ferritin (ng/mL)	r	-0.04	-0.02	-0.13	0.18
	p	0.80	0.91	0.46	0.33

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

4. Discussion

In IDA, which is the most common nutritional anemia, the Hb level is low and oxygen transport to the tissues and retinochoroidal circulation is impaired. Ocular manifestations such as retinal hemorrhages, retinal venous tortuosity, cotton-wool exudates, retinal vascular occlusion, nonarteritic ischemic optic neuropathy and disc edema are observed in IDA and the severity of the ocular signs were related to the severity of anemia [6,7]. Many pathogenetic factors such as anoxia, venous stasis, angiospasm, increased capillary permeability and decreased erythrocyte deformability secondary to hypoxia have been implicated in the retinopathy secondary to anemia [8–11]. Histotoxic anoxia may also develop due to the dysfunction of cytochrome oxidase, an iron containing enzyme [12]. Iron is an essential element for normal retinal physiology and particularly critical for the visual phototransduction cascade for isomerohydrolase activity and catalyzing the conversion of hydrogen peroxide to hydroxyl radical which is the most damaging of the reactive oxygen species. Antioxidant capasity decreases in iron deficiency and IDA [13]. It has also been shown that there is an inverse relationship between serum iron and the development of diabetic retinopathy [14]. Additionally, in recent studies it has been shown that choroidal thickness is also significantly reduced in iron deficiency anemia [15,16].

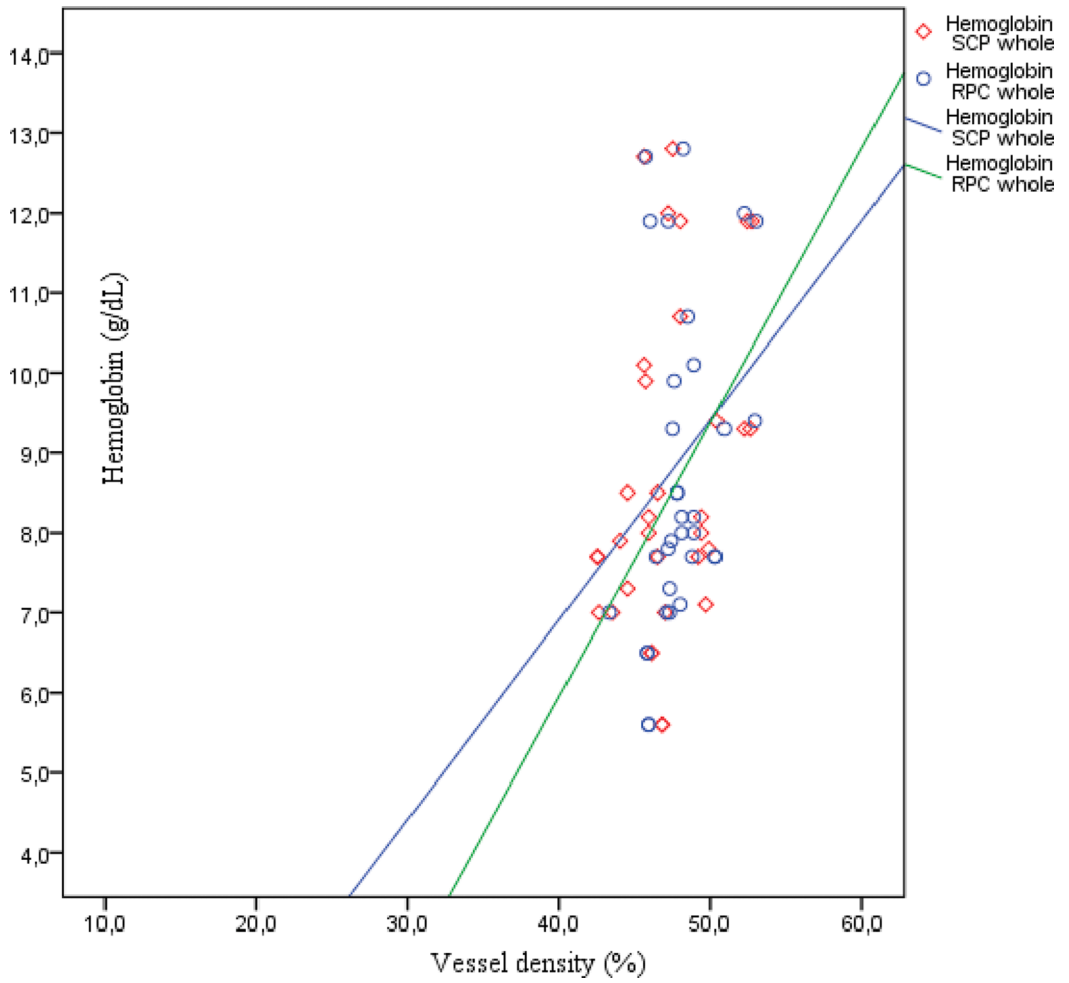

Fig. 1. Relationship between superficial capillary plexus (SCP) whole and radial peripapillary capillary (RPC) whole vessel density and mean hemoglobin. Scatterplot showing positive correlations between the mean hemoglobin and vessel density.

In the current study, we found that FD was significantly reduced in the IDA group, while there was no significant difference between the groups in terms of FAZ area and PERIM measurements. Korkmaz et al. reported that FAZ area, PERIM and FD were not different from the control group in their study evaluating a total of 32 children with IDA [17]. On the other hand, Duzgun et al. reported that FAZ, FAZ PERIM and FD values were significantly lower in the IDA group [18].

In both SCP and DCP macular vessel density analysis, we observed a significant reduction in all macular regions except fovea in IDA subjects. Similarly to our study, Korkmaz et al. showed a significant vessel density reduction in multiple regions of SCP. They also reported that the difference was not significant (except inferior parafovea and temporal perifovea), while vascular density was low in DCP [17]. Consistent to Korkmaz et al, Düzgün et al revealed that macular vessel density of the SCP in all parafoveal quadrants and the whole retina were significantly decreased while DCP vessel density showed statistically no significant difference in any parafoveal quadrant [18]. While the mean Hb level was 8.7 g/dL in our study, it was 10.3 g/d L and 9.4 g/dL in the studies of Korkmaz et al and Düzgün et al, respectively. More marked vascular density reduction may be explained by the lower mean Hb level and the more severe anemia in our study.

Iron is an essential micronutrient for normal myelination, oligodendrocyte biology and neurotransmitter synthesis. In IDA visual evoked potentials are impaired in infants and children [19,20]. It has been shown that specific iron-requiring enzymes such as glucose-6-phosphate dehydrogenase, dioxygenase, succinic dehydrogenase, and nicotinamide adenine dinucleotide hydride (NADH) dehydrogenase and cytochrome oxidase are more elevated in oligodendrocytes than in other brain cells [21]. Also, iron is a cofactor for cholesterol and lipid biosynthesis which is the precursor of myelin synthesis [22]. In a study by DeMaman et al, it was shown that iron was necessary for the maintanence of the optic nerve structure and iron repletion did not easily reverse optic nerve morphologic damage in anaemic rats [3]. Many recent studies in the literature have revealed that RNFL was thinned in IDA [23–25]. The RPC is a unique distinctive vascular network which is located parallel to the retinal ganglion cell axons within the RNFL around the optic disc and supply superficial RNFL. Hypoxia and impaired oxygen transport in IDA may also impair optic nerve blood flow.

In our study although RNFL thickness was lower in IDA group in peripapillary region and all four quadrants, the difference was not statistically significant. Peripapillary RPC vessel density was significantly decreased in whole image, peripapillary and superior-hemifield area compared to control group. Consistent to our study, Korkmaz et al. found that optic disc RPC small vessel density was significantly reduced in 4.5 × 4.5 mm optic disk scans. On the other hand, RNFL was not investigated in this study [17]. Kocer also demonstrated a significant optic disc vessel density decline in whole images, peripapillary, superior-hemi, inferior-hemi, inferiornasal, inferior-temporal, temporal-inferior, temporalsuperior, superior-nasal regions without reduction in RNFL thickness [26]. In correlation analysis, the FAZ area and DCP whole vessel density were not correlated with none of the hematalogic parameters including Hb, transferrin saturation, TIBC, serum iron and ferritin. SCP vessel density was positively correlated with Hb and serum

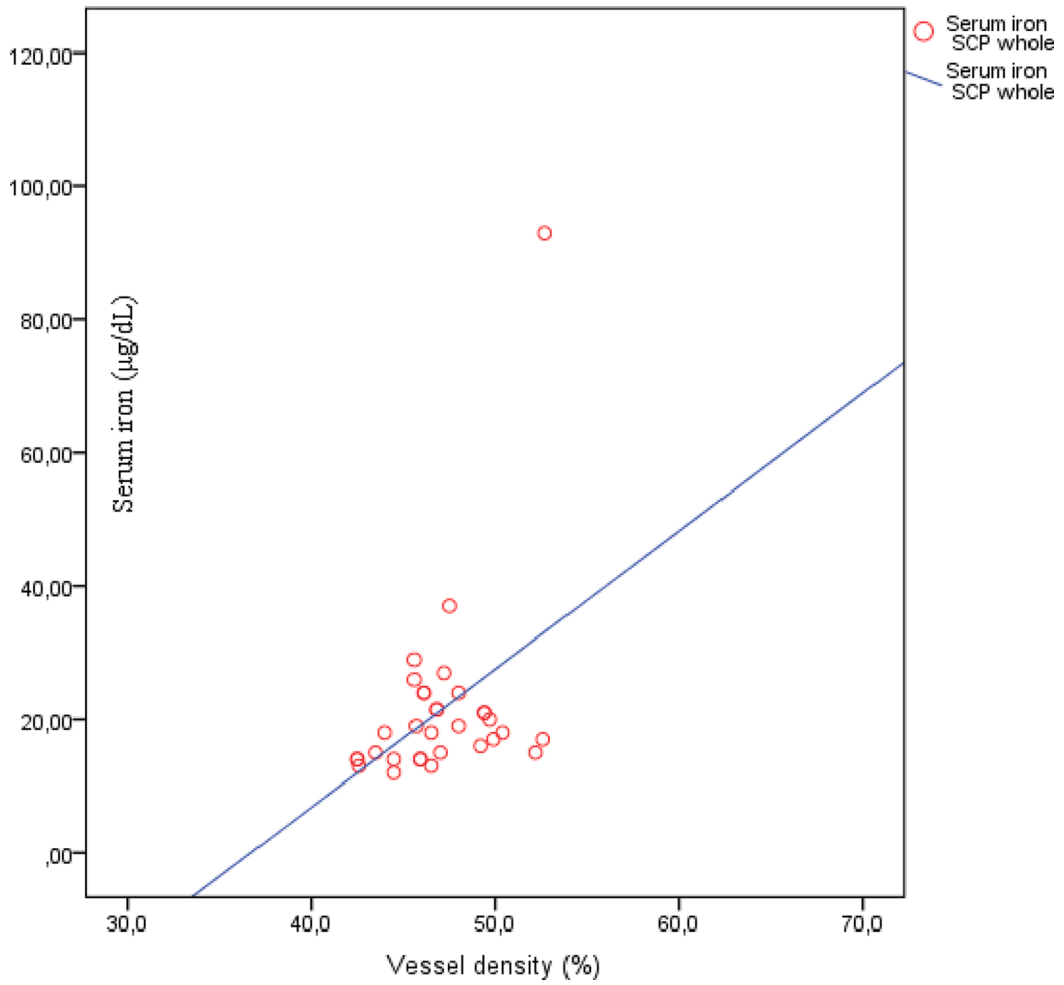

Fig. 2. Relationship between superficial capillary plexus (SCP) whole vessel density and serum iron. Scatterplot showing positive correlation between the serum iron and vessel density on SCP whole.

iron level. Positive significant association was also observed between Hb level and peripapillary RPC vessel density. Kocer et al reported correlation between RPC vascular density and hematological parameters, including Hb, HCT, MCV, MCH and ferritin [26].

The limitations of this study are relatively small sample size, lack of information on the onset and duration of IDA due to the repetitive nature; the changes in parameters have not been investigated after iron repletion treatment.

The pathophysiology of retinopathy related to anemia is still unclear and fundus examination is usually normal in cases with IDA. Based on current study we concluded that macular vascular density both in SCP and DCP was decreased and optic disc vascular density decreased without RNFL thinning in IDA patients. OCTA may be useful in detecting retinal ischemia before clinically visible signs of retinopathy associated with IDA. The mean Hb level and serum iron may be a predictive factor for reduction in macular and optic disc vessel density. Future large scale studies are worthwhile for establishing the benefit and role of vascular density reduction obtained by OCTA in understanding pathophysiology of anemia associated retinopathy and clinical management of IDA patients.

Declaration of Competing Interest

none

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