Original Article

Peripapillary retinal nerve fiber layer thickness in patients with iron deficiency anemia

Ipek Cikmazkara, Seyda Karadeniz Ugurlu

Purpose: To evaluate the effect of iron deficiency anemia (IDA) on peripapillary retinal nerve fiber layer (RNFL) thickness with optical coherence tomography (OCT). **Materials and Methods:** 102 female patients who had IDA (hemoglobin <12 g/dl, serum transferrin saturation <15%, serum iron <50 μg/dl, and serum ferritin <15 μg/dl) were enrolled in the study. Optic disc and RNFL parameters obtained by Cirrus high-definition OCT 4000 were compared with those of 49 age and sex-matched nonanemic individuals. The time between blood analysis and OCT measurements was 3.14 ± 5.6 (range, 0–28) days in the anemia group, and 3.5 ± 6.7 (range, 0–27) days in the control group (P = 0.76). **Results:** Average ages of 102 patients and 49 control subjects were 35.76 ± 10.112 (range, 18–66) years, and 36.08 ± 8.416 (range, 19–57) years (P = 0.850), respectively. The average RNFL thickness was 94.67 ± 9.380 in the anemia group, and 100.22 ± 9.12 in the control group (P = 0.001). Temporal, nasal, and lower quadrant average RNFL thicknesses of IDA group were thinner than the control group (P = 0.001, P = 0.013, P = 0.008). Upper quadrant RNFL thicknesses in IDA and control groups were similar. Correlation analysis revealed positive correlation between mean RNFL thickness and hemoglobin (r = 0.273), iron (r = 0.177), ferritin (r = 0.163), and transferrin saturations (r = 0.185), while a negative correlation was found between total iron binding capacity (r = −0.199) and mean RNFL thickness. **Conclusions:** Peripapillary RNFL thickness measured by OCT is thinner in adult female patients with IDA. It may have a significant influence on the management of many disorders such as glaucoma and neuro-ophthalmological diseases.

Key words: Iron deficiency anemia, optical coherence tomography, peripapillary retinal nerve fiber layer thickness

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Anemia is a widespread public health problem, and iron deficiency is the most common cause of anemia.[1] It may have deleterious effects in patients with various ocular diseases through enhancement of effects of ischemia.

Retina requires regular oxygen support so as to maintain its structural and functional integrity.[2] Inner retinal layers, which receive their blood supply from superficial and deep capillary plexus of the central retinal artery, are more susceptible to hypoxic alterations.[3] Retinal ischemia, a significant component of many visual disorders, has a significant role in development and progression of eye diseases such as diabetic retinopathy, retinal vascular occlusion, glaucoma, and retinopathy of prematurity.

Hypoxia causes neuronal death through various mediators and mechanisms. Retinal ganglion cells are known to be damaged by a reduction in normal perfusion and oxygen saturation.[4]

Oligodendrocytes, which have a critical role in myelination, require iron for the achievement of their normal functions.[5] Relative to other cerebral cells, specifically higher concentrations of iron-containing enzymes have been detected in oligodendrocytes.[6] Decrease in iron content during a certain period of rapid myelination can inhibit normal functioning of oligodendrocytes and prevent the development of myelination process.[5,7] On the other hand, previous studies demonstrated that brain functions evolved with improvement of anemia in patients with chronic renal disease, irrespective of the iron status of the affected individuals.[8] Iron deficiency has also been associated with dopaminergic dysfunction.[9] Deficiency of retinal dopaminergic dysfunction is thought to alter receptive area of axons and ganglion cells, which constitute retinal nerve fiber layer (RNFL).[10]

RNFL thickness measurement provides important clinical information for determination and differential diagnosis of diseases of optic nerve. Decreased thickness of RNFL has been demonstrated in various types of ischemic retinal diseases.[11-16] Reduction in RNFL thickness has been shown in diabetic patients based on optical coherence tomography (OCT) measurements.[11-14] Thinning of both macular and peripapillary RNFL in central or branch retinal artery occlusions have been documented.[15] In a study on patients with sickle cell anemia, focal macular thinning and thinner peripapillary RNFL on spectral-domain OCT (SD-OCT) was

Department of Ophthalmology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey

Correspondence to: Dr. Ipek Cikmazkara, Department of Ophthalmology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey. E-mail: ipekcintan@gmail.com

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reported.[16] Thinner RNFL was also shown in pediatric patients with anemia.[17,18]

In the current study, we aimed to evaluate the effect of iron deficiency anemia (IDA) on peripapillary RNFL thickness in adults with OCT.

Materials and Methods

Study design

The study has been conducted in accordance with the principles of the Helsinki Declaration and was approved by the local Institutional Review Board (February 27, 2014, #56). Consecutive patients who presented to the outpatient clinic were evaluated, and 102 female patients who fulfilled the inclusion criteria were enrolled in the study. IDA was diagnosed when serum hemoglobin was <12 g/dl, serum transferrin saturation <15%, serum iron <50 μg/dl, and serum ferritin <15 μg/dl.

Patients with best corrected visual acuity <20/20, lenticular or other ocular media opacities, history of intraocular operation or ocular trauma, glaucoma, uveitis, myopia or hyperopia over 4.0 diopters, amblyopia, retinal disorders, or intraocular pressure higher than 20 mmHg were excluded.

The control group was composed of 49 age and sex-matched nonanemic patients. The time between blood analysis and OCT measurements was 3.14 ± 5.6 (range, 0–28) days in the anemia group, and 3.5 ± 6.7 (range, 0–27) days in the control group ($P = 0.76$).

Outcome parameters

RNFL thickness was obtained with optic disc cube 200 × 200 scan protocol (Cirrus high-definition OCT [HD OCT] 4000, software version 6.5.0; Carl Zeiss Meditec, Inc. Dublin, CA, USA). Best scan with a signal strength >7 was used for the analysis. Average, temporal, nasal, superior, and inferior quadrant RNFL measurements were noted. Right eye values of the participants were used for statistical analysis.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Independent samples *t*-test was used for data with normal distribution, and Mann–Whitney U-test was employed for those without normal distribution. Correlation analysis was performed with Spearman's correlation test. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

Results

Among patients screened, 102 cases with IDA were included in the study. No attempt was made to determine the duration of IDA as reliable information was not provided by the majority of the patients.

Average ages of 102 patients, and 49 control subjects were 35.76 ± 10.112 (range, 18–66) years, and 36.08 ± 8.42 (range, 19–57) years ($P = 0.850$), respectively. Mean intraocular pressure of IDA and the control groups were 14.97 ± 2.47 mm/Hg and 15.16 ± 2.45 mm/Hg ($P = 0.654$), respectively.

The mean serum hemoglobin, serum iron, serum ferritin levels, serum transferrin saturation, and total iron binding capacity (TIBC) are presented in Table 1.

The average C/D ratio, rim and disc area, and cup volume were similar in both IDA and the control groups [Table 2].

The average RNFL thickness was 94.67 ± 9.38 in the anemia group, and 100.22 ± 9.12 in the control group ($P = 0.001$). Temporal, nasal, and lower quadrant average RNFL thicknesses of IDA group were thinner than the control group ($P = 0.001$, $P = 0.013$, $P = 0.008$). Difference between the upper quadrant RNFL thicknesses of the IDA and control group did not reach statistical significance; 116.63 ± 14.39 μm and 121.71 ± 15.19 μm ($P = 0.114$), respectively. RNFL thickness values are presented in Table 3.

Correlation analysis revealed positive correlation between mean RNFL thickness and hemoglobin, iron, ferritin, and transferrin saturations, while a negative correlation was found between TIBC and mean RNFL thickness [Fig. 1].

Discussion

IDA is the most frequently seen type of anemia worldwide.[19] The prevalence of IDA is estimated to be 3–5% in women, and

Table 1: Clinical characteristics of the groups

Characteristics	Anemic group (*n*=102)	Control group (*n*=49)	*P*
Hemoglobin (g/dl)	9.79±1.47	13.14±0.863	<0.001
Serum iron (μg/dl)	21.95±10.64	93.51±32.53	<0.001
Serum ferritin (μg/dl)	4.57±2.98	31.33±23.95	<0.001
Total iron binding capacity (μg/dl)	417.12±48.11	320.63±34.67	<0.001
Serum transferrin saturation (%)	5.39±2.84	29.39±10.43	<0.001

Table 2: Optic disc parameters of the groups

Optic disc pameters	Anemic group (*n*=102)	Control group (*n*=49)	*P*
Cup volume (mm^3)	0.12±0.11	0.14±0.20	0.426
Average C/D ratio	0.43±0.16	0.40±0.19	0.255
Rim area (mm^2)	1.48±0.21	1.54±0.28	0.137
Disc area (mm^2)	1.94±0.34	1.99±0.34	0.469

Table 3: Peripapillary retinal nerve fiber layer thicknesses of the groups

Peripapillary RNFL thickness	Anemic group (*n*=102)	Control group (*n*=49)	*P*
Average (μm)	94.67±9.38	100.22±9.12	0.001
Temporal (μm)	64.61±10.96	70.31±10.14	0.001
Superior (μm)	116.63±14.39	121.71±15.19	0.114
Nasal (μm)	72.17±11.55	77.73±12.36	0.013
Inferior (μm)	125.06±16.44	132.57±15.67	0.008

RNFL: Retinal nerve fiber layer

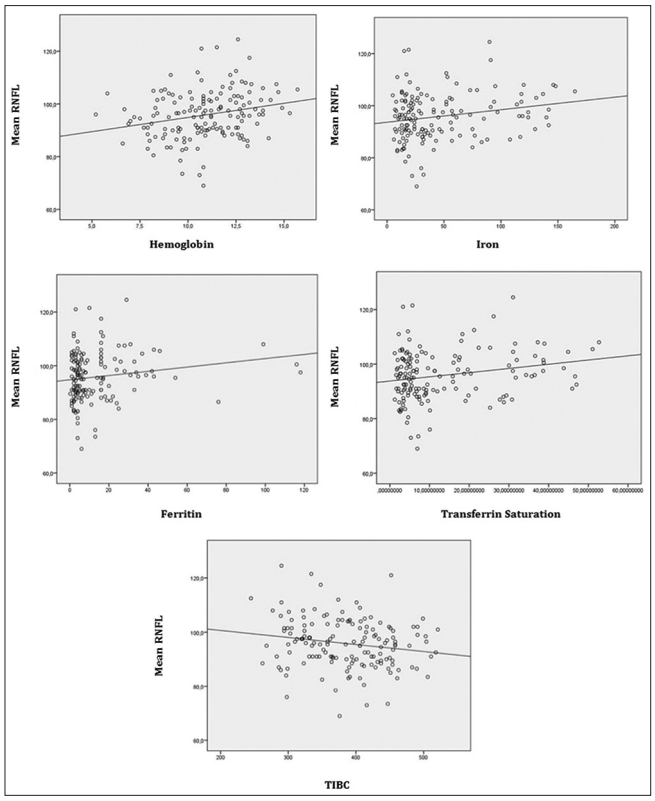

Figure 1: Correlation analysis between retinal nerve fiber layer thickness and laboratory findings of the groups

<1% in men. The incidence of iron deficiency with or without anemia was 12–16% in premenopausal women, and 2% in adult men in the USA.[20] In studies performed in the Turkish population, anemia was detected in 40–50% of the women in the childbearing age, most of which was related to iron deficiency.[21-23]

The current study studied peripapillary RNFL thickness in adults with IDA. Three male patients with IDA had presented during the study; given the scarcity of male patients, a decision to limit the study to female patients was made.

Oncel Acir *et al*. has recently reported that peripapillary RNFL is thinner in the nasal-inferior quadrant in patients with IDA.[24] They examined 73 eyes of 39 patients with IDA and 68 eyes of 34 age and sex-matched healthy subjects. All subjects in both groups were females. Average RNFL thicknesses were similar in the IDA (84.4 ± 5.9) and control groups (85.3 ± 4.5). Peripapillary RNFL was significantly thinner only in nasal-inferior quadrant in patients with IDA. Macula ganglion cell-inner plexiform layer (GCL+) measurements revealed similar values in both groups. Weak correlation was detected between serum ferritin level and peripapillary RNFL thickness in the temporal superior area.

Two other previous studies investigated RNFL thickness in patients with IDA; however, these studies were conducted in pediatric patients.[18,25] Türkyilmaz *et al.* detected decreased mean, upper and lower RNFL thickness using SD-OCT (Cirrus HD SD-OCT) in 40 pediatric patients compared to controls.[18] The average hemoglobin values of the study and the control group were 8.9 ± 1.7 g/dl and 12.9 ± 0.6 g/dl, respectively. Statistically significant correlation was detected between mean RNFL, upper, lower, and temporal quadrant RNFL thickness and average values of hemoglobin. There were no significant correlations between peripapillary RNFL thicknesses and the other hematologic parameters in the anemic group.

Aksoy *et al*., used spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) to investigate pediatric control subjects (n = 59), patients with thalassemia major (n = 47), and IDA (n = 22).[25] They found lower RNFL thickness in the inferior quadrant in IDA group and detected a correlation between RNFL thickness and hemoglobin level. In the thalassemia major group, RNFL was thinner in all four quadrants compared to the control and IDA group. In their study, hemoglobin levels were 7.36 ± 1.62 g/dl and 14.86 ± 0.99 g/dl, and serum ferritin levels were 6.50 ± 2.48 µg/dl and 17.37 ± 2.23 µg/dl in the IDA and the control groups, respectively.

In the current study, 102 adult patients with IDA and 49 control patients were investigated. Mean hemoglobin value was (9.79 ± 1.46 g/dl) higher and mean serum ferritin value (4.57 ± 2.97 µg/dl) was lower than in the studies by Aksoy *et al*., and Türkyılmaz *et al*., and was similar to the values in the study by Oncel Acir *et al*., Our patient group had lower serum iron and transferrin saturation, and higher TIBC values compared to the study of Türkyılmaz *et al.*

Our average RNFL thickness values obtained in IDA (94.67 ± 9.38 µm), and control groups (100.22 ± 9.12 µm) were slightly thinner than the results of Türkyilmaz *et al*., (98.6 ± 5.6 µm vs. 102.0 ± 5.2 µm).[18] The study by Oncel Acir *et al*. reported 96.6 ± 7.9 µm in IDA and 99.5 ± 8.6 in the control group. All three studies had used Cirrus HD SD-OCT. However, average RNFL thickness values obtained with Spectralis were much thicker (study group: 184.0 ± 31.14 µm vs. control group: 187.73 ± 27.36).[25]

Recent studies performed in the pediatric age group have detected thicker RNFL when compared with the adult age group.[26-31] In a study performed by Barrio-Barrio *et al.* Cirrus OCT was used and mean RNFL thickness was found as 97.4 ± 9.0 µm. This value was slightly higher than the values in Cirrus database.[26] Yanni *et al*., and Turk *et al*., detected thicker mean RNFL thickness in healthy pediatric individuals using Spectralis OCT.[30,31] All of these studies indicate presence of a slightly thicker RNFL in the pediatric age group. This phenomenon explains the observation of thinner mean RNFL thicknesses in our patient and control groups. Besides, in none of the studies we reviewed, RNFL values as high as those obtained by Aksoy *et al*., were encountered.

In the current study, average RNFL, temporal, nasal, and lower quadrant RNFL thicknesses were thinner when compared to the nonanemic group. Positive correlations were detected between hemoglobin levels and various hematologic parameters, and mean RNFL, temporal, nasal and lower quadrant RNFL thicknesses. While Oncel Acir *et al*., failed to detect any correlation between RNFL thickness and hematologic parameters except for RNFL thickness in clock hour 10 sector and serum ferritin level,[24] two above-mentioned pediatric studies reported higher correlation coefficients compared to ours. Detection of lower correlation coefficients may be related to the factors such as decreased RNFL thickness with advanced age, milder degrees of anemia in the current

study group, and more severe reflection of effects of anemia on RNFL in younger age. Wider age spectrum of our study group relative to other studies might have affected the outcomes obtained, too. Although the correlation is not strong, we still demonstrated statistically significant difference between RNFL thicknesses of both groups. This finding suggests that IDA may lead to remarkable changes on RNFL.

One of the main limitations of our study is that we did not know how long the patients had been anemic. It is, however, not possible to know the duration of anemia precisely. The patients might have been asymptomatic for a long time, and/or anemia could have been detected during a regular check-up. Another important shortcoming of the study is the patient group; it was composed of merely young female patients. This approach might fall short of determining effects of anemia on RNFL in male patients and elderly.

RNFL analysis has a significant role in diagnosis and follow-up of many disorders such as glaucoma. IDA appears to result in thinning of peripapillary RNFL; it is; however, not known whether peripapillary RNFL thinning is associated with iron deficiency, anemic hypoxia or both. Prospective, randomized studies will contribute to better characterization of the changes imposed by IDA on RNFL, and to determination of potential effects of treatment.

Conclusion

Peripapillary RNFL thickness measured by OCT is thinner in adult female patients with IDA. It may have a significant influence on the management of many disorders such as glaucoma and neuro-ophthalmological diseases.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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