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Analysis of retinal nerve fibre layer thickness and optic disc parameters in patients of iron deficiency anaemia

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ABSTRACT

Background: To evaluate peripapillary retinal nerve fibre layer (RNFL) thickness and optic disc parameters in iron deficiency anaemia (IDA) patients and its correlation with various blood parameters of age and sex matched healthy controls with the help of spectral domain optical coherence tomography (SD-OCT).

Materials and methods: Cross sectional, hospital based study was done on patients with IDA and healthy patients attending departments of Ophthalmology and haematology of a tertiary referral hospital in Eastern India from June 2020 to January 2021. Comprehensive ophthalmic examination was done in all patients. Peripapillary RNFL thickness was measured using SD-OCT. Blood analysis for all patients included blood haemoglobin, serum iron binding capacity, Serum Ferritin, total iron binding capacity (TIBC), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin Concentration (MCHC).

Results: Twenty five patients with IDA and 25 age and sex matched healthy patients constituted the study and control groups respectively. Mean age of study and control groups was 40.44±5.51 and 39.12±11.60 years respectively. Strong positive correlation was noted between mean RNFL thickness and haemoglobin, serum ferritin, serum iron and serum transferrin levels. Negative correlation was noted between mean RNFL thickness and total iron binding capacity.

Conclusion: Patients with IDA in Eastern India have decreased mean peripapillary RNFL thickness. Mean RNFL thickness in different quadrants may not only be dependent on iron parameters but might also be influenced by dietary and geographical factors.

Introduction

Anaemia is a common public health problem, iron deficiency being the most common cause.[1] Women of child bearing age are particularly affected.[2] Iron is required for carrying oxygen and for normal functioning of oligodendrocytes, which play an important role in myelination.[3,4] Hence, depleted iron stores cause hypoxia and defective myelination. Hypoxia results in neuronal death through various mediators and mechanisms. As a result, retinal ganglion cells undergo damage by a compromise in normal perfusion and oxygen saturation.[5] Iron deficiency also results in dopaminergic dysfunction.[6] Retinal dopaminergic dysfunction alters receptive areas of axons and ganglion cells, which constitute retinal nerve fibre layer (RNFL).[7]

Decreased thickness of RNFL has been reported in various types of ischemic retinal diseases like diabetic retinopathy,

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glaucoma, retinal vascular occlusion, and retinopathy of prematurity. Thus decreased RNFL thickness has played a key role in diagnosis and monitoring of these diseases.[8-10] Optical coherence tomography (OCT) is a non-invasive imaging method that is widely used in the diagnosis of optic nerve and RNFL diseases.[11] The spectral domain OCT (SD OCT) technique provides faster acquisition, better resolution and improved imaging of retinal morphology than traditional OCT.[12]

In the current study, we aimed to evaluate peripapillary RNFL thickness and optic disc parameters in iron deficiency anemia (IDA) patients and its correlation with various blood parameters of age and sex matched healthy controls with the help of SD-OCT.

Materials and methods

The present study included 25 eyes of 25 adults between 20-55 years of age with iron deficiency anaemia and 25 eyes of 25 age matched healthy control subjects who had come for routine check-up procedure to Department of Ophthalmology and Hematology at a tertiary care hospital in Eastern India between June 2020 to January 2021. The study adhered to the basic tenets of Helsinki Declaration. Institutional ethical committee clearance was obtained prior to beginning the study. Informed consent was obtained from all patients before enrolling into the study.

IDA was diagnosed when serum haemoglobin (Hb) was <10 g%, serum (Sr) iron ≤50µg/dl, Sr Ferritin concentration ≤15 g µ/dl, Mean Corpuscular Volume(MCV) <80 fl/red cell and Total iron binding capacity (TIBC) ≥300. Patients with best corrected visual acuity less than 20/20, myopia or hypermetropia >4.0 D, lenticular or other ocular media opacities, evidence of glaucoma ,strabismus, history of intraocular surgery or ocular trauma, uveitis, diabetic retinopathies, vitro retinal disorders,, neurologic diseases or any systemic diseases other than IDA were excluded from the study.

A complete ophthalmologic examination was done including visual acuity assessment using Snellen's visual Acuity chart, refraction, detailed slit lamp examination for anterior segment evaluation, intra ocular pressure (IOP) measurement by Goldmann applanation tonometry and dilated fundoscopy with indirect ophthalmoscope and 20 Dioptre lens. Blood analysis for all patients included serum Hb, serum iron binding capacity, Serum Ferritin, total iron binding capacity (TIBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin Concentration (MCHC).

Outcome Parameters

Topcon 3D SD OCT-1 Maestro (Topcon Medical System, Tokyo, Japan) was used to obtain RNFL thickness in peripapillary region using OCT 3D optic disc cube 200×200 scan protocol. The signal strength used for analysis was >7. Average, temporal, nasal, superior and inferior quadrant RNFL measurements were noted along with disc area, rim area and Cup disc ratio. Right eyes of all the patients were arbitrarily taken for analysis.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences version 25. 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. Youden's index was calculated. $p<0.05$ was considered statistically significant.

Results

The present study included 25 patients with IDA in the study group and 25 normal patients in the control group. The mean age of study group was 40.44±5.51 (range 20-60) years. Mean age of the control group was 39.12±11.60 (20-60) years. The clinical and laboratory characteristics of cases and controls are presented in Table 1. There was no significant difference in the age, refractive status and IOP in both the groups. Significant differences were noticed in gender, Hb%, Sr Iron, Sr Ferritin, Sr Transferrin, TIBC, MCV, MCH, and MCHC.

The average disc area, rim area, cup disc ratio were same in both the study and control groups. There was no significant difference between the two groups (Table2). RNFL thickness values are presented in Table 3. There was a statistical significant difference noted in average RNFL thickness as well as RNFL thickness in superior, inferior and nasal quadrants between the two groups.

Table 1 Clinical and laboratory characteristics of the groups.

Characteristics	Study (n= 25)	Control (n= 25)	*p value*
Age	40.44±14.06	37.36±12.83	0.421
Gender			
Male	8	13	0.003
Female	17	12	
Refraction	1.12±0.52	1.17±0.42	0.459
IOP	12.487±1.808	12.607±1.827	0.81587
Hb	6.68±1.98	13.20±1.32	<0.001
Serum Iron	24.5±9.78	86.31±8.44	<0.001
Serum Ferritin	5.03±1.40	36.63±2.82	<0.001
TIBC	416.2±103.24	318.36±7.91	<0.001
Serum Transferrin	5.34±1.47	30.19±1.37	<0.001
MCV	68.79±10.33	87.89±2.41	<0.001
MCH	21.56±4.77	29.24±2.08	<0.001
MCHC	32.26±9.36	34.16±1.77	<0.001

IOP: intraocular Pressure, Hb: hemoglobin, TIBC: total iron binding capacity, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration.

Table 2 Optic disc parameters of the patients and control groups.

Characteristics	Study (n= 25)	Control (n= 25)	*p value*
Rim Area	1.48±0.28	1.55±0.302	0.400
Disc Area	1.98±0.42	1.97±0.39	0.915
Cup: Disc ratio	0.43±0.16	0.40±0.19	0.255

On Correlation analysis, a strong positive correlation was noted between mean RNFL thickness and Hb, Sr Iron, Sr Ferritin and Sr Transferrin while a negative correlation was observed between mean RNFL thickness and TIBC (Table 4) (Figure 1). Positive correlation noted between superior RNFL thickness with Sr Hb, Sr Iron and Sr ferritin (r=0.16, 0.05, 0.03) Similarly positive correlation was also found between inferior RNFL thickness and Sr Hb (r=0.22). We also found a positive correlation between nasal RNFL thickness and Sr Ferritin (r=0.362).

Table 3 Peripapillary retinal nerve fibre layer thickness by SD OCT.

RNFL thickness	Study (n= 25)	Control (n= 25)	*p value*
Average RNFL thickness	85.52±13.3	105.2±4.78	<0.001
Superior quadrant	102.88±26.29	137.44±5.45	<0.001
Inferior quadrant	102.8±23.63	129.08±1.85	<0.001
Nasal quadrant	64.24±14.89	86.24±2.44	<0.001
Temporal quadrant	60.8±15.91	67.8±5.04	0.045

RNF: retinal nerve fibre layer.

Table 4 Correlation between average RNFL layer and various blood parameters.

Average RNFL thickness 95.36± 14.02 µ	Mean±SD	Correlation "r"	*p value*
Hb	9.94±3.7	0.892	<0.001
Serum Ferritin	20.8±16.1	0.770	<0.001
Serum Iron	55.4±32.5	0.688	<0.001
Serum Transferrin	17.76±12.63	0.695	<0.001
TIBC	367.28±87.71	-0.368	0.009

RNFL: retinal nerve fibre layer, Hb: hemoglobin, TIBC: total iron binding capacity.

Receiver operating characteristic (Roc analysis) shows area under the curve is 0.891 (95% ci 0.78-0.99) with a p<0.001. Youden's index was calculated. Thus, at cut off value of 97 µm of total thickness of retinal nerve fibre, sensitivity is 100% and specificity is 84% of detecting anemia.

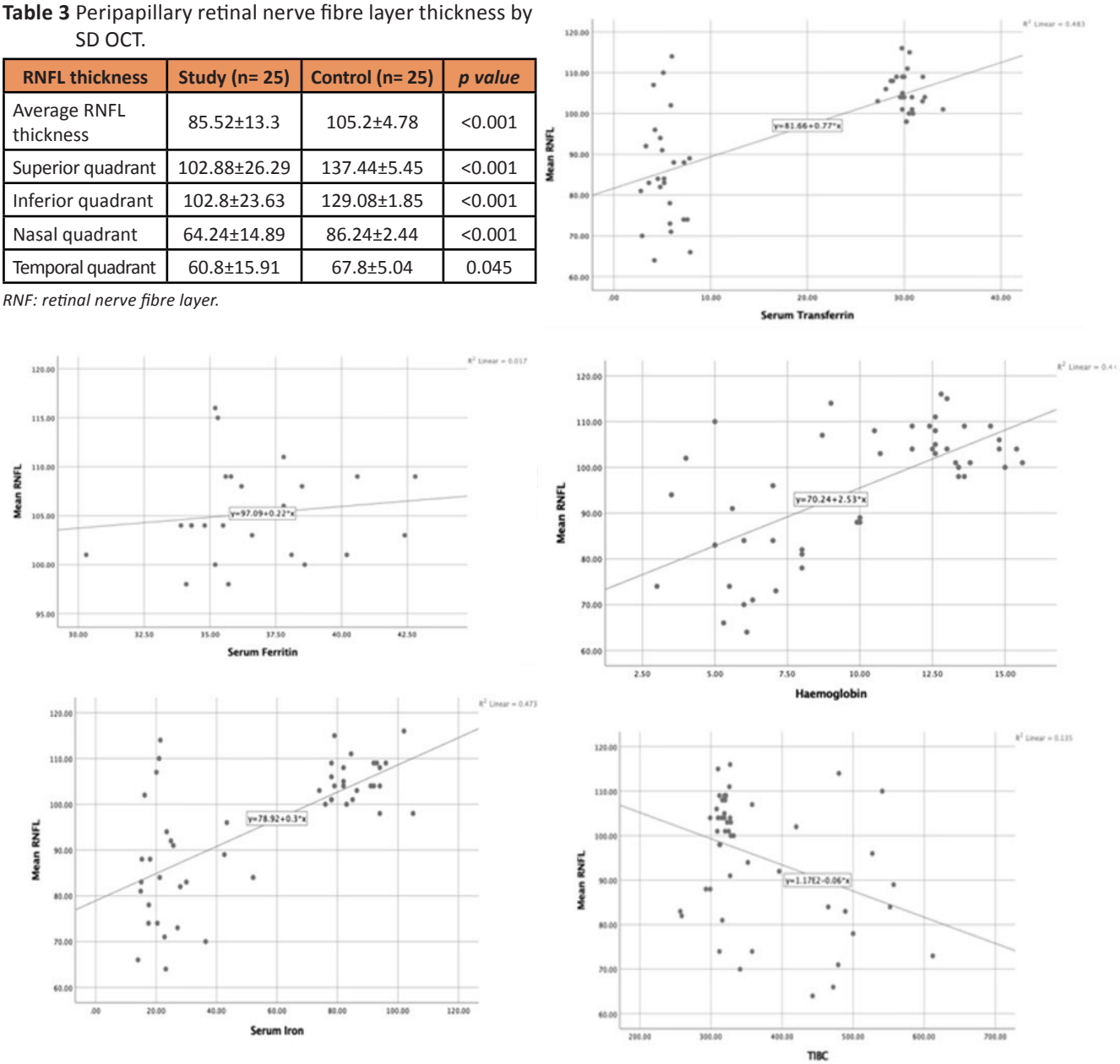


Figure 1. *Correlation analysis between retinal nerve fibre layer thickness and laboratory findings of the group.*

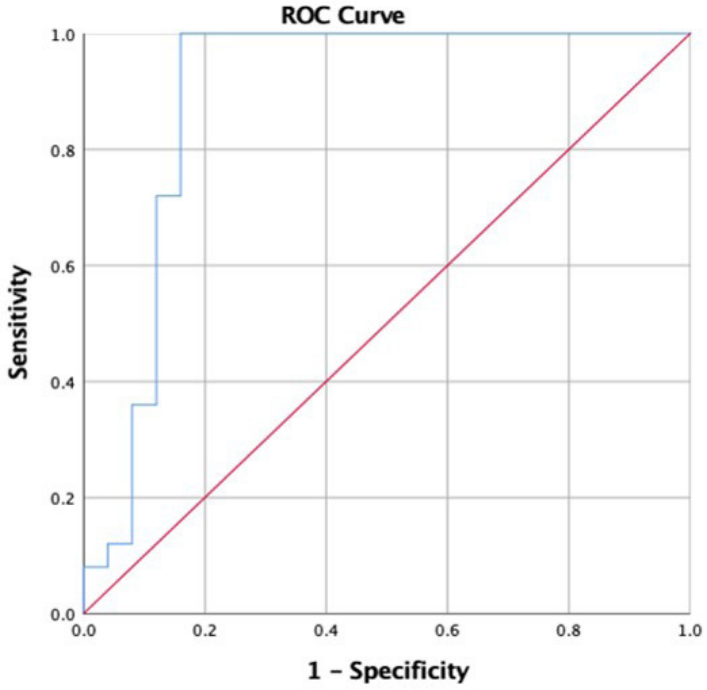


***Figure 2**. ROC Analysis.*

Discussion

IDA has been found to be the most prevalent type of anaemia worldwide.[13] It is known to cause various ocular diseases due to ischaemia.8 Decreased thickness of RNFL has been demonstrated in various ischaemic retinal diseases.[14] In our study, we have evaluated the RNFL thickness and optic disc parameters in patients with IDA. A significant (p<0.003) female preponderance was seen in our study which corroborated with other studies.[8, 15, 16] Several studies conducted in Turkish population have detected anaemia in 40-50% of the women in the childbearing age, most of which was related to iron deficiency.[17,18]

In our study mean serum Hb value (6.68±1.98 gm %) was lower and mean Serum Ferritin (5.03±1.40) was higher than in studies by Cikmazkara I *et al*[8] and Akdogan E *et al*.[16] However, Jaiswal S *et al*[3] have reported a lower mean haemoglobin and Sr Ferritin as compared to our study. Cases in our study had a higher mean Sr Iron (24.5±9.78) than that reported by Cikmazkara I *et al*.[8] However, TIBC and Sr Transferrin were similar between the two studies. Low range of Sr Hb in our study could be attributed to the direct referral of patients from Hematology Department who already had moderate to severe anemia.

Average disc area, rim area and cup disc ratio did not show any statistical significance which was similar to those reported by Cikmazkara I *et al*.[8] In our series we found IDA patients had significantly (p<0.001) thinner average, superior, inferior and nasal quadrant when compared to healthy controls. Maximum thinning was seen in nasal quadrant and maximum thickness was noted in the superior quadrant. Previous study in adult females with IDA by Moussa Eltohamy[2] showed thinning in average, superior, inferior, nasal and temporal quadrants. Study conducted by Jaiswal S. *et al*[3] on patients with IDA showed a decrease in peripapillary RNFL thickness in all four quadrants.

Various ophthalmic diseases like glaucoma are also associated with RNFL thinning along with changes in Optic Nerve Head.[19, 20] Hence, a thorough history regarding iron deficiency is vital for these disorders while taking OCT for RNFL analysis and management of such patients. Myopia and glaucoma are associated with optic nerve head changes and RNFL thining.[19, 21, 22] We could not find any significant optic nerve head changes except RNFL changes, so this should be considered while analysis of patients.

On correlation analysis between average and quadrant wise RNFL thickness with various laboratory parameters, we found a strong positive correlation between mean RNFL thickness and Sr Hb, Sr Iron, Sr Ferritin and Sr Transferrin while a negative correlation is found between mean RNFL thickness and TIBC. Positive correlation between superior RNFL thickness with Sr Hb ,Sr Iron and Sr Ferritin was noted. A positive correlation was also found between inferior RNFL thickness and Sr Hb .We also found a positive correlation between nasal RNFL thickness and Sr Ferritin. Strong correlation may be related to severe degree of anemia in our study, hence reflecting the effect of anemia on RNFL.

Cikmazkara *et al*[8] also reported a positive correlation between mean RNFL thickness and Sr Hb, Sr Iron, Sr Ferritin, and transferrin saturations, while a negative correlation was found between TIBC and mean RNFL thickness similar to us. Jaiswal *et al*[3] have reported a positive correlation between average RNFL thickness and Sr Hb and serum ferritin, and a

negative correlation was seen with TIBC. Whereas, Moussa Eltohamy[2] have reported a positive correlation between mean RNFL, Sr Hb and Sr Iron. All this studies have only compared the average RNFL with blood parameters. Akdogan *et al*[16] reported significant correlations between inferior quadrant RNFL thickness and Hb, and between nasal quadrant RNFL thickness and Sr Iron and Sr Ferritin concentrations, and TIBC which is similar to ours.

Our study has certain limitations. It has small sample size and is a hospital based study confined to Eastern India and so it does not represent typical population of India. Hence, the results of the study cannot be generalised. Larger studies from different regions are required to confirm the results obtained from our study and enhance the clinical importance of these findings. Further, duration of iron deficiency and history of blood transfusion were not taken into consideration. Moreover, the patients were not subdivided into various groups based on severity of anaemia. It is a cross sectional study and RNFL thickness was not revaluated after iron supplementation. Further studies are required to determine whether these RNFL changes can be reversed after treatment.

Conclusion

On assessment of the peripapillary RNFL thickness and optic disc parameters in IDA patients in Eastern India and comparing it to controls, it was seen that the average RNFL thickness in IDA decreases but quadrant wise it varies in different regions and is not only dependent on iron parameters but might also on dietary and geographical factors.

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Conflict of interest

The authors declared no conflict of interest.

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