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Association between Serum Ferritin and Primary Open-angle Glaucoma: A Retrospective Cross-sectional study

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Abstract

Background: Oxidative damage has a significant contribution to the development of Primary Open-Angle Glaucoma (POAG). Accumulation of Iron in the human body increases Oxidative stress significantly. Serum Ferritin concentration gives accurate insight into Iron stores in the human body. Ferritin is considered a preferred marker for assessing the oxidative stress caused by Iron.

Objectives: To study the Association between Serum Ferritin levels and Primary Open-Angle Glaucoma.

Methods: This was a hospital-based cross-sectional study. The study included recently diagnosed 196 patients with Primary Open-angle Glaucoma. Study participants were divided into 3 groups based on Intra Ocular Pressure (IOP). Group 1 – Mild group with IOP 21-30 mmHg, Group 2 - Moderate group with 31 – 50 mmHg. Group 3 – Severe group with >51 mmHg. Serum Ferritin levels were statistically compared in all the 3 study groups.

Results: Overall analysis showed a highly statistically significant association (P-Value 0.00) in Serum Ferritin concentration between Mild, Moderate, and Severe Primary Open-Angle Glaucoma. groups.

Conclusion: Our study found a direct association between serum Ferritin levels and the severity of Primary Open-Angle Glaucoma. Association was strong in the severe group of Primary Open-Angle Glaucoma in both male and female populations. We found that higher

serum ferritin level was associated with significantly higher chances of Glaucoma diagnosis.

Keywords: Serum Ferritin, Primary Open-Angle Glaucoma, Oxidative stress, Iron, Intra Ocular Pressure.

Introduction

Glaucoma is a condition where intraocular pressure increases significantly causing damage to the optic nerve and loss of vision. It is the third most common reason for irreversible blindness in India [1]. As per a study done in 2020 [2], India has 12 million Glaucoma patients and 1.5 million patients with blindness. Still, 75% are undiagnosed [1,2] in India. They represent the submerged portion of the Iceberg. The global burden of Glaucoma was estimated to be 3.54% [3] and India was found to be 2.3 – 4.7 % [4,5] in the year 2020. Glaucoma is presented as a progressive Visual field defect that slowly causes Tubular vision with loss of peripheral vision associated with structural damage to the Optic disc [6]. Primary Open-angle Glaucoma (POAG) has a higher prevalence than primary angle-closure glaucoma in India [7]. POAG is a multifactorial disease with a diverse range of causative factors [8.9.10].

Many studies done in India and abroad showed Oxidative damage had a significant contribution to the development of POAG [11,12,13]. Oxidative stress and free radicals accumulation cause damage to the trabecular meshwork present in the iridocorneal angle. as trabecular meshwork is the main pathway for Aqueous humor drainage, Intra Ocular Pressure (IOP) raises causing Open-Angle Glaucoma. Oxidative stress can also damage retinal Ganglion cells and can cause cell death and Optic nerve damage. This will contribute to vision loss by Glaucoma.

There has been considerable interest in the role of Iron in Oxidative damage to several organs. Iron is a mineral required by the human body for various bodily functions. It is required for the synthesis and functioning of Haemoglobin, Myoglobin, and as a co-enzyme of many Biochemical functions. Iron is stored in a specialised protein called Ferritin in the liver, Spleen, Small intestine, etc [21]. Serum Ferritin concentration gives accurate insight into Iron stores in the human body. Iron accumulation in the body has been associated with aging, Oncogenesis, and neurodegenerative disease progressions like Parkinson's disease and Alzheimer's disease. Accumulation of Iron also increases Oxidative stress. Ferritin is considered a preferred marker for assessing the oxidative stress caused by Iron [22,23].

Materials and methods

This was a hospital-based cross-sectional study. The study included recently diagnosed 196 patients with Primary Open-angle Glaucoma (POAG). These were the patients who attended the Ophthalmology OPD of the Institution for 1.5 years from 15.01.2021 to 15.07.2022. Study participants were divided into 3 groups based on Intra Ocular Pressure (IOP). Group 1 – Mild group with IOP 21-30 mmHg, Group 2 - Moderate group with 31 – 50 mmHg. Group 3 – Severe group with >51 mmHg. The study protocol was approved by the ethics committee of the Institution. Written Informed consent was obtained from all the study participants to use any clinical data for research.

Subjects were recently diagnosed patients with Open-angle Glaucoma. All the test subjects were aged 18 years or higher. The anterior chamber angle was open. Visual fields with any one or both eyes with Glaucomatous damage or Intra Ocular Pressure (IOP) >21 mmHg without any Visual field defect were selected. If both eyes of the same patient were affected by POAG, the eye with the maximum IOP was selected for the study.

Exclusion criteria included patients with conditions that affect Visual field tests other than Glaucoma such as Diabetic retinopathy, Hypertensive Retinopathy, Age-

related macular degeneration, and Stroke. Patients with Glaucoma under treatment, Normotensive Glaucoma, Pseudo exfoliative syndrome, Secondary Glaucoma, patients who underwent cataract or Refractive surgery, retinitis pigmentosa, and acute systemic illness were excluded from the study.

Detailed clinical history was taken from all the subjects who participated in the study. Details including age, sex, blood sugar, and associated systemic complications like Neuropathy, Nephropathy, Hyperlipidemia, and Hypertension were noted. Complete ocular examination was done in the department of Ophthalmology, including Best corrected visual acuity, Intra Ocular Pressure (IOP), Anterior segment examination using slip lamp biomicroscope with 90D lens, Detailed Fundus examination, and Visual field examination. After obtaining Informed consent from the subject, 5 mL of the blood sample was collected from all subjects under aseptic conditions. Blood was tested for Serum Ferritin (Chemiluminescence) in Snibe maglumi 800 Chemiluminescence analyser. Serum Ferritin Reference Range in males was 20-250 ng/mL and in female were 10-120 ng/mL. due to this vast difference, both categories were analysed and studied separately.

Data were analysed using IBM SPSS Statistics Version 21.0 and MS Excel 2007. Qualitative variables were expressed as frequency and percentages. Quantitative variables were expressed in Mean and Standard deviations. The student unpaired test was used for a two-group mean comparison. For all statistical analyses, P <0.05 was considered statistically significant.

Results

Study participants were divided into 3 groups and studied separately Gender wise. The gender-wise independent study was needed because the Normal Reference range of Serum Ferritin in Male was 20 - 250 ng/ml and in female were 10 - 120 ng/ml. Table 1 shows the Mean, Standard Deviation (SD), P-Value of Age, and Serum Ferritin. Table 2, 3, and 4 shows Gender wise analysis of the variables. A total of 83 subjects with Mild POAG were selected for the study among which 45 (54.2%) were male and 38 (45.8%) were female subjects. A total of 65 subjects with Moderate POAG were selected for the study among which 34 (52.3%) were male and 31 (47.7%) were female subjects. In the case the of Severe POAG group, 48 subjects were selected, among which 26 (54.2%) were male subjects and 22 (45.8%) were female subjects. The Mean age with the Standard deviation of the Mild group was 50.82±5.04. The moderate Group was found to be 52±4.1. The severe Group had 50.81±5.9. P-Value was found to be 0.29 and not significant. This confirmed that all three groups were age and Gender matched. The Mean±SD (Standard deviation) of Serum Ferritin in the Mild group was found to be 52.98±26.2 ng/ml. Gender-wise analysis among the Mild group showed Mean±SD in Male subjects as 74.93±12.1 ng/ml and Female subjects as 26.97±8.2 ng/ml. The P-Value of Gender analysis was 0.00 and highly significant. The Mean±SD (Standard deviation) of Serum Ferritin in the Moderate group was found to be 112.58±46.02 ng/ml. Gender-wise analysis among the Moderate group showed Mean±SD in Male subjects as 154.91±12.45 ng/ml and Female subjects as 66.16±9.4 ng/ml. The P-Value of Gender analysis was 0.00 and highly significant. Association was the same in the Severe group also. The Mean±SD (Standard deviation) of Serum Ferritin in the severe group was found to be 175.42±65.7 ng/ml. Gender-wise analysis among the Severe group showed Mean±SD in Male subjects as 234.08±13.9 ng/ml and Female subjects as 106.09±11.8 ng/ml. The P-Value of Gender analysis was 0.00 and highly significant. Overall analysis showed a highly

significant association (P-Value 0.00) in Serum Ferritin concentration between Mild, Moderate, and Severe POAG groups. Table 5 showed post-HOC analysis between different variables.

Table 1: Mean, Standard Deviation, F Value, and P-Value of Age and Serum Ferritin

		Number	Mean	Std. Deviation	Std. Error	F-Value	P-Value
Age	Mild	83	50.82	5.037	.553	1.227	0.295
	Moderate	65	52.00	4.096	.508		
	Severe	48	50.81	5.884	.849		
	Total	196	51.21	4.983	.356		
Serum Ferritin	Mild	83	52.98	26.206	2.876	113.754	0.000
	Moderate	65	112.58	46.015	5.707		
	Severe	48	175.42	65.714	9.485		
	Total	196	102.73	66.416	4.744		

Std: Standard; P<0.05 was considered significant, P- 0.000** is considered highly significant; Table is Original.

Table 2: Gender wise analysis of Mean, SD, t-Value, and P-Value of Age and Serum Ferritin in Mild group

	Gender	Number	Mean	Std. Deviation	Std. Error Mean	t Value	P-Value
Age	Male	45	51.11	5.175	.771	0.572	0.569
	Female	38	50.47	4.914	.797		
Serum Ferritin	Male	45	74.93	12.099	1.804	20.737	0.000
	Female	38	26.97	8.195	1.329		

SD: Standard Deviation; Std: Standard; P<0.05 was considered significant, P- 0.000** is considered highly significant; Table is Original.

Table 3: Gender wise analysis of Mean, SD, t-Value, and P-Value of Age and Serum Ferritin in Moderate group

	Gender	Number	Mean	Std. Deviation	Std. Error Mean	t Value	P-Value
Age	Male	34	52.62	4.185	.718	1.279	0.203
	Female	31	51.32	3.953	.710		
Serum Ferritin	Male	34	154.91	12.450	2.135	32.137	0.000
	Female	31	66.16	9.445	1.696		

SD: Standard Deviation; Std: Standard; P<0.05 was considered significant, P- 0.000** is considered highly significant; Table is Original.

Table: 4: Gender wise analysis of Mean, SD, t-Value, and P-Value of Age and Serum Ferritin in the severe group

	Gender	Number	Mean	Std. Deviation	Std. Error Mean	t Value	P-Value
Age	Male	26	51.77	5.361	1.051	1.231	0.224
	Female	22	49.68	6.387	1.362		

Serum Ferritin	Male	26	234.08	13.879	2.722	34.013	0.000
	Female	22	106.09	11.844	2.525		

SD: Standard Deviation; Std: Standard; P<0.05 was considered significant, P- 0.000** is considered highly significant; Table is Original.

Table 5: Post HOC analysis between different variables.

Dependent variable	(i) group	(j) group	Mean difference (i-j)	Std. Error	P-value
Age	Mild	Moderate	-1.181	.824	.154
		Severe	.007	.903	.994
	Moderate	Mild	1.181	.824	.154
		Severe	1.188	.947	.211
	Severe	Mild	-.007	.903	.994
		Moderate	-1.188	.947	.211
Serum Ferritin	Mild	Moderate	-59.609*	7.491	.000
		Severe	-122.441*	8.201	.000
	Moderate	Mild	59.609*	7.491	.000
		Severe	-62.832*	8.607	.000
	Severe	Mild	122.441*	8.201	.000
		Moderate	62.832*	8.607	.000

Std: Standard; P<0.05 was considered significant, P- 0.000** is considered highly significant; Table is Original.

Discussion

Our study showed a highly significant association (P-Value 0.00) in Serum Ferritin concentration between Mild, Moderate, and Severe POAG groups. Gender-wise analysis done in each group also showed a highly significant association (P-Value 0.00) between its Male and Female subjects. This scenario was seen in all three study groups. Our study findings were in line with the study conducted by Wang SY et al [29,30] in the United States of America which explained the importance of Iron metabolism in the pathogenesis of Glaucoma. In the study by Wang SY et al, higher serum ferritin levels were significantly associated with a higher prevalence of Glaucoma. The study by Lin SC et al [31,] conducted on the South Korean population, also revealed the same findings.

Ferritin is a globular storage protein of Iron in the human body. It stores iron and releases it in a controlled fashion as per body requirements. Ferritin also acts as a Carrier of Iron in blood and an indirect marker of iron stores in the human body [24], which is more appropriate than serum Iron concentration. Ferritin also chelates free iron and protects from oxidative stress. Increased ferritin concentration increases ferritin iron content. It causes potential adverse effects via redox reactions [27,28]. Ferritin is regarded as the preferred marker for the assessment of Iron related oxidative stress compared to other iron-related Biomarkers [22,23].

Even though Iron is an important mineral for many cellular functions, excess storage produces hydroxyl radicals which cause DNA damage and degenerative organ damage. Increased IOP and severity of Visual field defects in Glaucoma parallel with the degree of oxidative damage in Trabecular Meshwork (TM) cells. There is substantial evidence that Oxygen radicals cause the pathogenesis of POAG. In vitro studies, [32.33] showed that Iron regulation is important in Glaucoma Pathogenesis through Retinal Ganglion and TM cells. The study by Lin et al [33] showed potential biological mechanisms for redox-active Iron. The study demonstrated Chronically stressed TM cells due to elevated Iron content in a hyperoxic model. The study also found changes in the expression of Iron homeostasis genes. Chelation of Intracellular Iron, protected cells from oxidative stress-induced apoptosis. TM cells in the Glaucomatous eye had additional protection from oxidative stress. It is due to increased expression of endothelial-leukocyte adhesion molecules. It's a cytokine involved in complex antioxidative pathways [34].

Potential Bias was limited in the study. Patients were picked up based on the disease criteria. The primary researchers were a trained Ophthalmologist and a Trained Biochemist. The generalisability of the study was limited as the study had been done in a hospital setting. This study recommends Ophthalmologists check Serum Ferritin levels, especially in Severe POAG patients. This can help Ophthalmologists with better and more Comprehensive treatment protocols for Primary Open-Angle Glaucoma.

Conclusion

Our study found a direct association between serum Ferritin levels and the severity of POAG. Association was strong in the severe group of POAG in both male and female populations. We found that higher serum ferritin level was associated with significantly higher chances of Glaucoma diagnosis. We concluded that serum Ferritin levels should be considered by Ophthalmologists during the Treatment of Primary Open-Angle Glaucoma for better comprehensive treatment.

Limitations

Our study was a cross-sectional study done at the hospital level. This limited our ability to understand the exact mechanism at the community level. Our study population was limited to 196 cases. A more detailed study is required with more study population selected at the community level from Urban and Rural populations from various parts of India.

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