



ASSOCIATION OF SERUM FERRITIN LEVELS WITH GRADES OF HYPERTENSIVE RETINOPATHY

Ophthalmology

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ABSTRACT

Introduction: To study the correlation of serum ferritin levels with grades of hypertensive retinopathy. **Methods:** Our case control study included 200 individuals, above the age of 40 years. Patients were divided into three groups: Group 1 with normotensive patients, Group 2 with patients with hypertension only and Group 3 with patients with hypertensive with hypertensive retinopathy. Patients in group 3 were further divided into 4 grades depending upon the Grading of hypertensive retinopathy according to Keith-Wagener-Barker (KWB) classification. **Result:** For sex stratified ferritin levels, all the females in Group 2 & Group 3 (100.0% each) and majority of females in Group 1 (54.5%) had ferritin >200 ng/ml. For sex stratified ferritin levels, all the males in Group 2 & Group 3 (100.0% each) had ferritin >300 ng/ml whereas on the other hand all the males in Group 1 (100.0%) had ferritin ≤300 ng/ml. Increasing trends of mean ferritin levels with increase in severity of grades of hypertensive retinopathy was seen. **Conclusion:** A positive association of serum ferritin level with hypertensive retinopathy was observed as higher levels of serum ferritin corresponded with higher grades of hypertensive retinopathy. We also conclude that not only serum ferritin levels, but other factors like family history and duration of illness is also proportionate with severity of hypertension and hypertensive retinopathy.

KEYWORDS

Serum ferritin, Hypertensive retinopathy, Keith-Wagener-Barker (KWB) classification

Introduction

High blood pressure (BP) is ranked as the third most important risk factor for attributable burden of disease in south Asia (2010)¹. Hypertension (HTN) exerts a substantial public health burden on cardiovascular health status and healthcare systems in India. About 1.39 billion adults worldwide had hypertension in 2010, but the recent projections estimate a 30% increase in this prevalence by the year 2025, exposing nearly 2 billion individuals to risk of hypertension and associated comorbidities².

Hypertensive retinopathy (HR) is a condition characterized by a spectrum of retinal vascular signs in people with elevated blood pressure (BP)³. Even though the pathophysiological mechanism of HR is not fully established, a strong correlation between signs of hypertensive retinopathy with blood pressure levels had been reported^{4,5} along with other pathogenic mechanisms, such as increased oxidative stress⁶.

Ferritins belong to a family of highly conserved supra-molecular protein nanostructures found in virtually all life forms and is of major importance because it helps in storing iron safely and reversibly⁷. Serum ferritin is the main protein performing the important function of regulation of iron homeostasis in the human body. The level of serum ferritin is a useful clinical biomarker of the amount of iron that is stored in the body⁸.

Serum ferritin levels and the prevalence of hyperferritinemia are increased in men with hypertension compared with normotensive healthy individuals⁹, this study was conducted to find out the association of serum ferritin levels with hypertension and hypertensive retinopathy.

Material and methods

Our case control study included 200 individuals, above the age of 40 years. An informed consent was obtained from all the patients and clearance for carrying out the study was obtained from the Institutional Ethical Committee, Era's Lucknow Medical College & Hospital, Lucknow.

Patients were divided into 3 groups as group 1 with normotensive patients, group 2 with patients with hypertension only and group 3 with patients with hypertensive with hypertensive retinopathy.

Patients in group 3 were further divided into 4 grades depending upon the Grading of hypertensive retinopathy according to Keith-Wagener-Barker (KWB) classification. Grade I included 33 patients with grade I HR, grade II had 35 patients with grade II HR, grade III had 27 patients with grade III HR and grade IV had 5 patients with grade IV HR.

Exclusion Criteria: Patients with co-existing medical illness such as diabetes mellitus, hepatic or/and renal disease, cardiac/cerebral illness, hemoglobinopathies, porphyria, dyslipidemia, recent major surgery or illness. Patient with any ocular media opacity, history of anti-epileptic drug intake Patients with Age <40 years. Patients not giving consent for inclusion in the study.

Eligible subjects underwent a comprehensive assessment including documentation of medical history, physical examination, and measurement of the laboratory variables. The physical examination included systolic and diastolic BP measurement with the subjects sitting after a 5-minutes rest using a sphygmomanometer.

Ophthalmological assessment of the patients were done. BCVA was measured using Snellen's chart for both the eyes, followed by Torch light examination, indirect ophthalmoscopy, slit lamp examination, fundus evaluation by direct ophthalmoscope and fundus photography by Zeiss fundus camera. Intraocular pressure (IOP) was measured using Goldmann's Applanation Tonometer.

Grading of hypertensive retinopathy was done according to Keith-Wagener-Barker (KWB) classification⁷.

Serum ferritin estimation was done using Calbiotech- ELISA kit. Statistical Analysis: Data was analysed using SPSS 21.0 package. ANOVA and independent samples 't'-test were employed.

Table I- Blood pressure, Age group & Gender distribution among different grades of hypertensive retinopathy.

S No.	Parameters	Subgroup	Group 1		Group2		Group3	
			No.	%	No.	%	No.	%
1	Blood pressure	Normal (<120 and <80)	18	36.0	17	34.0	14	14.0

		Prehypertension (SBP 120-139) (DBP 80-89)	15	30.0	7	14.0	17	17.0
		High blood pressure Hypertension Stage 1 (SBP -140-159) (DBP- 90-99)	17	34.0	23	46.0	49	49.0
		High blood pressure Hypertension Stage 2 (SBP- >=160) (DBP- >=100)	0	0.0	3	6.0	20	20.0
2	Age groups	40-49 years (79)	29	58.0	22	44.0	28	28.0
		50-59 years (64)	18	36.0	14	28.0	32	32.0
		60-69 years (40)	3	6.0	11	22.0	26	26.0
		≥70 years (17)	0	0.0	3	6.0	14	14.0
3	Sex	Female (113)	22	44.0	36	72.0	55	55.0
		Male (87)	28	56.0	14	28.0	45	45.0

SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), MAP (Mean Arterial Pressure),

Table II: Mean Blood Pressure distribution in 3 groups

SN	Blood Pressure (mm Hg)	Group 1 (n=50)		Group 2 (n=50)		Group 3 (n=100)		ANOVA	
		Mean	SD	Mean	Mean	SD	SD	F	'p'
1	SBP	123.84	8.39	130.12	15.44	140.36	17.89	20.861	<0.001
2	DBP	82.56	6.48	83.80	7.53	89.46	10.94	11.871	<0.001
3	MAP	96.32	6.34	99.24	8.34	106.46	12.54	18.686	<0.001

SBP were elevated sharply in Group 3 as compared Group 2 and Group 1 (140.34±17.89 vs. 130.12±15.44 vs. 123.84±8.39 mmHg).

DBP were elevated in Group 3 as compared Group 2 and Group 1 (89.46±10.94 vs. 83.80±7.53 vs. 96.32±6.34 mmHg).

MAP were elevated in Group 3 as compared Group 2 and Group 1 (106.46±12.54 vs. 99.24±8.34 vs. 96.32±6.34 mmHg).

Table III. Mean Blood Pressure distribution in grades of hypertensive retinopathy

SN	Blood pressure	Grade I (n=33)		Grade II (n=35)		Grade III (n=27)		Grade IV (n=5)		ANOVA	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	'p'
1	SBP	127.09	12.55	140.35	12.96	153.70	17.35	161.60	19.19	19.99	<0.001
2	DBP	82.06	6.26	88.54	5.78	97.61	13.00	108.04	16.65	16.04	<0.001
3	MAP	97.07	7.64	106.78	6.87	116.42	13.93	127.07	21.20	21.07	<0.001

SBP were elevated sharply in Grade IV as compared with Grade III, II & I (156.34±17.16 vs. 153.70±17.35 vs. 140.35±12.96 vs. 127.09±12.55 mmHg).

DBP were elevated in Grade IV as compared with Grade III, II & I (98.00±13.04 vs. 97.78±13.61 vs. 88.8±5.54 vs. 82.06±6.26 mmHg). MAP were elevated in Grade IV as compared Grade III, II & I (117.33±13.82 vs. 116.42±13.93 vs. 9106.78±6.87 vs. 97.07±7.64 mmHg).

Table IV: Distribution of Ferritin levels in 3 groups

Gender	SN	S. Ferritin levels (ng/ml)	Total	Group 1 (n=50)		Group 2 (n=50)		Group 3 (n=100)	
				No.	%	No.	%	No.	%
Female (n=113)	1	≤200	10	10	45.5	0	0.0	0	0.0
	2	>200	103	12	54.5	36	100.0	55	100.0
$\chi^2=45.380$; $p<0.001$									
Male (n=)	1	≤300	28	28	100.0	0	0.0	0	0.0
	2	>300	59	0	0.0	14	100.0	45	100.0
$\chi^2=87.000$; $p<0.001$									

For sex stratified ferritin levels, all the females in Group 2 & Group 3 (100.0% each) and majority of females in Group 1 (54.5%) had ferritin >200 ng/ml. Statistically, a significant difference was observed among the groups for ferritin level in females.

For sex stratified ferritin levels, all the males in Group 2 & Group 3 (100.0% each) had ferritin >300 ng/ml. on the other hand all the males in Group 1 (100.0%) had ferritin ≤300 ng/ml. Statistically, a significant difference was observed among the groups for ferritin level in males.

Increasing trends of mean ferritin levels with increase in severity of grades of hypertensive retinopathy was seen.

Table V: Distribution of Ferritin levels in grades of retinopathy

Gender	SN	S. Ferritin levels	Total	Grade I		Grade II		Grade III		Grade IV	
				No.	%	No.	%	No.	%	No.	%
Female (n=55)	1	≤200	0	0	0.0	0	0.0	0	0.0	0	0.0
	1	>200	55	18	100.0	20	100.0	14	100.0	3	100.0
Male (n=45)	1	≤300	0	0	0.0	0	0.0	0	0.0	0	0.0
	2	>300	45	15	100.0	15	100.0	13	100.0	2	100.0

All females irrespective of retinopathy grades had ferritin levels ≤200ng/ml. All males irrespective of retinopathy grades had ferritin levels >300ng/ml.

Discussion

Hypertension is characterized by persistently high blood pressure (BP) in the systemic arteries. A positive family history is a frequent occurrence in patients with hypertension, with the heritability estimated between 35% and 50% in the majority of studies¹⁰. Vascular changes due to systemic hypertension can be most clearly observed in the eye, of which hypertensive retinopathy is the most commonly occurring¹¹.

Various biomarkers have been studied to predict poor outcomes and progression of retinopathy and hypertension. Of which, Serum ferritin was found in common pathophysiological processes, including oxidative stress and lipid peroxidation, which are important to the pathogenesis and development of insulin resistance and the metabolic syndrome. This study was done to find out the association of serum ferritin level with grades of hypertensive retinopathy.

In our study the age of study population ranged between 40-85 years of age and the mean age was 53.51 ±9.60 years and majority of patients were females (55%), which was similar to a study done by Omotoso *et al.* (2016)¹² and their study reported mean age of 58.9 years and majority of females (77.7%).

In our study, Among the grades of retinopathy, majority of patients with Grade IV, II & III were Stage I hypertensives (60.0%, 51.9% & 65.7% respectively), while majority of patients with grade I retinopathy (69.7%) were normal or pre-hypertensive. Statistically a significant association between increasing severity of retinopathy with hypertension was observed. This result was similar to a study done by Shah *et al.* (2013)¹³ in which 48.4% of the cases had grade I hypertensive retinopathy & 31.8% cases of the cases had grade II hypertensive retinopathy, while grade III was seen in 16.1% cases & the remaining 3.6% had grade IV hypertensive retinopathy. Shafi *et al.*

(2016)¹⁴ reported most common grade of retinopathy among their study was population was grade II (41.2%), followed by grade I (31.3%), I (21.6%) & IV (5.8%).

In the present study, we also found association of hypertensive retinopathy with duration of hypertension. Shantha *et al.* (2009)¹⁵ in their study also reported a significant association of retinopathy and duration of hypertension. Omotoso *et al.* (2010)¹² also reported a similar finding of strong association between duration of hypertension and retinopathy.

SBP, DBP and MAP were most elevated in grade IV retinopathy. Statistically, a significant association between elevated blood pressure parameters with retinopathy grades was observed and this result corresponded with a study done by Amanda D. Henderson,¹⁶ they reported higher blood pressure in individuals with higher grades of hypertensive retinopathy.

In our study among the males with hypertensive retinopathy, grade IV had highest mean ferritin (464.50±36.06 ng/ml), followed by grade III (395.92±46.31 ng/ml), grade II (378.53±15.37 ng/ml), grade I (341.40±16.48 ng/ml). Among females with hypertensive retinopathy, also grade IV had highest mean ferritin (375.00±15.00 ng/ml), followed by grade III (325.36±28.18 ng/ml), grade II (267.20±9.86 ng/ml), grade I (237.72±14.96 ng/ml).

Coban *et al.* (2010)¹⁷ in their study reported significantly elevated ferritin levels in higher grades of hypertensive retinopathy (92.9±31.8 ng/ml) as compared to lower grades of hypertensive retinopathy (77.8±23.7 ng/ml) and controls (59.9±19.2 ng/ml).

A study by Singh *et al.* (2020)¹⁸ also reported elevated ferritin in hypertensive patients (293.27±219.84 ng/ml) as compared to non-hypertensives (72.23±29.75 ng/ml). Although both the above studies had reported elevated serum ferritin levels, but the mean ferritin observed in the present study was much higher than the reported levels in other studies.

Conclusion

The present study showed a positive association of serum ferritin level with hypertensive retinopathy, as higher levels of serum ferritin corresponded with higher grades of hypertensive retinopathy. We also conclude that not only serum ferritin levels, but other factors like family history and duration of illness is also proportionate with severity of hypertension and hypertensive retinopathy. The behavior of serum ferritin in patients with severe COVID-19 and high mortality rates in patients with high ferritin levels necessitated further investigations to understand the role of ferritin in various diseases [19].

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