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ORIGINAL RESEARCH ARTICLE

SERUM BIOMARKERS OF LIPID, ATHEROGENIC INDEX OF PLASMA, ELECTROCARDIOGRAM AND FUNDUS CHANGES IN HYPERTENSIVE PATIENTS OF CENTRAL NEPAL

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ABSTRACT

Background: Hypertensive retinopathy, its ocular complication, is characterized by progressive metabolic disorders and structural damage to the retina. Lipids play an essential role in retinal hemostasis. The study was aimed to assess the prevalence of hypertensive retinopathy, the association between traditional lipid biomarkers and hypertensive retinopathy, and the predictive risk for future cardiac events using the atherogenic index of plasma in hypertensive patients of central Nepal.

Methods: A hospital-based cross-sectional study was conducted in the Department of Ophthalmology, Chitwan Medical College, from 15 August 2021 to 30 October 2021. Ethical clearance was taken from the Institutional Review Committee (Ref: CMC-IRC/078/079-025). Convenience sampling was done to reach the sample size. Relevant data was entered in a proforma specified for the study. Data analysis was done using Statistical Package for the Social Sciences version 26, point estimate at 95% Confidence Interval (CI) was calculated along with frequency and proportion for binary data, p-value <0.05 was considered statistically significant.

Results: The prevalence of hypertensive retinopathy was 34 (10.7%) (7.5-14.6 at 95% CI) in the study subjects. Gender wise females 167 (52.7%) outnumbered the males 150 (47.3%). Serum cholesterol level was the only biomarker significantly associated with the development of hypertensive retinopathy (p = 0.01). The mean atherogenic index of plasma in the study subjects was high (0.52).

Conclusions: The prevalence of hypertensive retinopathy was lower in this study than similar studies done elsewhere. The atherogenic index of plasma was higher in the study subjects.

INTRODUCTION

Hypertension (HTN) affects approximately 50 million individuals in the United States and approximately one billion worldwide.[1] Recent data from the Framingham Heart Study suggest that individuals who are normotensive at age 55 have a 90 percent life time risk for developing hypertension.[2] The pathophysiology of Hypertensive retinopathy (HR) is not yet well understood however dyslipidemia may play a contributory role. One study from Nepal has shown increased level of LDL in HR.[3-5] It is evident now, there is strong evidence that signs of HR have a powerful correlation with blood pressure levels.[6-8] However, high blood pressure cannot be fully responsible for all pathological mechanisms that leads to the development of retinopathy, being stipulated the implication of additional processes and factors like inflammation, abnormal angiogenesis, endothelial dysfunction, oxidative stress etc.[5,9-14]

Dyslipidemia is an important modifiable risk factor for HTN.[15] The photoreceptor cells outer segment membranes are extremely labile to oxidation as they contain high levels of polyunsaturated fatty acids.[16] Retinal dysfunctions and degeneration are constantly associated with either overabundance or deficiency of specific lipids within retinal cells.[17] So far, little research has focused on the role of lipids and lipoproteins in various retinal diseases.

The study aimed to find out the prevalence of hypertensive retinopathy (HR), the association between hypertensive retinopathy and traditional lipid biomarkers, and the predictive risk for future cardiac events using atherogenic index of plasma (AIP) in hypertensive patients of central Nepal.

METHODS

This hospital-based cross-sectional study was conducted in Chitwan Medical College (CMC) - Teaching Hospital in the Department of Ophthalmology. After obtaining ethical clearance from Institutional Review Committee (IRC) (Ref: CMC-IRC/078/079-025), the study was carried out from 15 August 2021 to 30 October 2021.A convenient sampling method was used to calculate the sample size.

$$\frac{z^2_{1-\alpha/2}p(1-p)}{e^2}$$

Sample size (n) = Cochran (1977)

Where

n= minimum required sample size

Z = 1.96 at 95% confidence interval

P = prevalence reported by a similar study

e =margin of error 5%

In a study conducted by Vaidya A et al[18] the prevalence of hypertension in urban areas of Kathmandu was approximately 25% in the year 2007, taking the value the sample size of the study would be,

Sample size= $1.96^2 \times 0.25\ (1-0.25)/0.05^2 = 0.72/0.0025 = 288$

With 10% non-respondents in the study the sample size for the study was 317.

After explaining the purpose of the study and confidentiality of data collection, informed verbal and written consent was obtained from each participant. Participants were requested to fill in the standard proforma related to demographic data, previous spectacle use, and family history of hypertension (HTN). Study subjects with metabolic conditions like diabetes, severe somatic comorbidities, renal and neurological pathologies, glaucoma, diabetic retinopathy, acute and chronic uveitis, and non-consenting study subjects were excluded in this study.

A detailed ocular examination was done including the recording of visual acuity by using Snellen's letter chart. All hypertensive patients referred from the department of Medicine or directly visiting the department of Ophthalmology underwent the following examinations in the following sequence: visual acuity measurement of each eye separately (unaided and with a pin-hole), extra-ocular movement assessment, cover test, cover-uncover test, refraction using a Heine Beta 200 retinoscope, anterior segment examination with a slit lamp, and dilated fundus examination using an indirect ophthalmoscope using +90 D Volk lens, Tropicamide eye drops were used for fundus dilatation. Keith Wagener and Baker's classification of Hypertensive Retinopathy[4] and Modified Schie's classification was used to grade the HR status.[5] The participants were advised to investigate their serum biomarkers of lipids profile viz. triglyceride (TG), total cholesterol (TCL), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and electrocardiogram (ECG) in the department of Medicine.

The atherogenic index of plasma (AIP) was calculated using the following formula.[19]

AIP = Log (TG/HDL- Total Cholesterol)

AIP<0.11 - low risk

AIP (0.11 - 0.21) intermediate risk

AIP>0.21 increased risk

Data collection was meticulously was done by the faculty, residents, and intern doctors of the Department of Ophthalmology and Department of Medicine and entered in a specified proforma. Data thus collected were entered into SPSS version 26 for statistical analysis. Data were presented as percentages and mean (standard deviation). Descriptive statistical analysis was done for a mean (standard deviation), and frequency was applied for percentages to find out the prevalence, p-value of 0.05, and less was considered significant where the associations were measured. A statistician was consulted when necessary.

RESULTS

In the current study, 317 study participants were enrolled, 634 eyes were examined in detail. The prevalence of hypertensive retinopathy was 34 (10.7%), 95% CI (7.5-14.6) in the study. Gender wise females 167 (52.7%) outnumbered the males 150 (47.3%) (Table 1).

Table 1: Prevalence and grading of Hypertensive Retinopathy (HR) in the study subjects

Grading of hypertensive retinopathy (HR) in the study subjects	Frequency (%)
Normal*	283 (89.3
Slight narrowing, sclerosis, and tortuosity of the retinal arterioles; mild, asymptomatic hypertension - **Grade I**	30 (9.5)
Definite narrowing, focal constriction, sclerosis, and AV nicking - **Grade II**	1 (0.3)
Retinopathy (cotton-wool patches, arteriolosclerosis, hemorrhages) – **Grade III**	1 (0.3)
Neuroretinal edema, including papilledema; Siegrist streaks, Elschnig spots – Grade **IV**	2 (0.6)
Total	**317 (100)**

*Majority of the study subjects had no hypertensive retinopathy changes

Mean age of the study subjects was 53.9 years (+- 13.5), mean waist circumference of the study subjects was 93.0 cms (+- 10.6), and mean total cholesterol level was 177.2, whereas mean atherogenic index of plasma in the study population was 0.52 (Table 2).

Table 2: Mean value of risk factors associated with hypertensive retinopathy in the study subjects

Variables	Mean±SD, (Min. - Max.)
Age in years	53.9±13.5 (21 - 84)
Waist circumference in centimeters	93.0±10.6 (61 - 139)
Body Mass Index (BMI)	25.3±4.7 (12 - 45)
Total Cholesterol level in mg/dl	177.3± 45.5 (67 - 400)
Triglycerides mg/dl	169.5± 92.0 (46 - 845)
Serum High density lipoproteins mg/dl	46.3±6.9 (20 - 73)
Serum low density lipoproetins mg/dl	101.3± 30.2 (41 - 300)
Log (TG/HDL - T. Cholesterol), Atherogenic Index of Plasma	0.52±0.2 (0.03 - 1.30)
Total Study Subjects	**317**

Majority of the participants, 313 (98.7%) had intermediate to high risk level of atherogenic index of plasma for predictive future cardiac event (Table 3).

Table 3: Study subjects in different risk category according to atherogenic index of plasma values

Risk category	Frequency (%)
Low risk	4 (1.3)
Intermediate risk	7 (2.2)
High risk	306 (96.5)
Total	**317 (100)**

In the present study, 279 (88%) subjects had normal electrocardiogram findings (Table 4).

Table 4: Electrocardiogram changes in the study participants

Electrocardiogram (ECG) findings	Frequency (%)
Sinus rhythm, Normal	279 (88.0)
ECG changes indicating ischaemic heart disease	17 (5.4)
Right bundle branch block	2 (0.6)
Left bundle branch block	1 (0.3)
Left ventricular dysfunction	2 (0.6)
Poor (R) wave progression	4 (1.3)
Right ventricular hypertrophy	2 (0.6)
Left ventricular hypertrophy	3 (0.9)
Other ECG changes	4 (1.3)
Sinus bradycardia	3 (0.9)
Total	**317 (100)**

Association of serum biomarkers of lipids with hypertensive retinopathy (HR) was seen only with total cholesterol level. There was no association between body mass index (BMI) with atherogenic index of plasma (Table 5).

DISCUSSION

In the current study, 317 study subjects were included, 634 eyes were examined in detail. Females 167 (52.7%) outnumbered the male subjects. The mean age of presentation of the study subjects was 53.9 ± 13.5 years. The overall prevalence of hypertensive retinopathy in our study was 34 (10.7%). The male, female distribution of hypertension was nearly equal in the current study with the females just outnumbering the males. This finding of the study was not comparable with studies done by Choi et al[20] and Bastola et al,[3] where the prevalence of hypertension was reported high in males. Similarly, the current study had a lower prevalence of hypertensive retinopathy when compared with studies done by Bastola et al,[3] and Besharati et al[21] which reported a prevalence of 54% and 39.9% of hypertensive retinopathy respectively of different grades in similar settings. The lower prevalence of hypertensive retinopathy in the current study could be attributed to change in health-seeking behavior of the patients and excellent control of hypertensive status.

In the present study, except for serum cholesterol level values, none of the biomarkers of serum lipids were significantly associated with the development of hypertensive retinopathy. In addition, the values for serum biomarkers in the present study were borderline or slightly raised (Table 2, Table 5). This finding of the study was comparable with a study done by Wong et al.[22] Though these findings were not comparable with the study done by Bastola et al,[3] where all the biomarkers of lipids were associated significantly with hypertensive retinopathy. In the current study, the mean atherogenic index of plasma was 0.52, and the majority of the study subjects had a predictive risk to develop future cardiac events. This was attributed to the fact that the study subjects comparatively had lower serum HDL levels and higher serum TG levels. The atherogenic index of plasma has been a predictive biomarker used widely to predict cardiac problems in known cases of hypertension.[12] To our knowledge this study is the first of its kind exploring the atherogenic index of plasma in hypertensive patients to predict future cardiac events from Nepal.

In the current study, 38 (12%) of the study subjects had a spectrum of electrocardiographic (ECG) changes varying from ischaemic heart disease 17 (44.7%) the commonest to sinus bradycardia. The findings of silent ECG changes in our study were comparable to the study done by Bastola et al[3] in a similar setting in Nepal, however, in the latter study, the prevalence of silent ECG changes in hypertensive patients was 28 (28%). The lower prevalence of silent ECG changes in our study is contributed by the facts like relatively well-controlled serum biomarkers of lipids and good control of hypertensive status.

Mean body Mass Index (BMI) and mean AIP in our study were 25.3±4.7 (12- 45) and .52±0.20 (0.03–1.30) respectively, however a significant association was not seen between these variables (p = 0.7). This finding of our study was not comparable with a study done in Nepal by Kharel et al,[23]

Table 5: Association between serum biomarkers of lipids and hypertensive retinopathy and atherogenic index of plasma (AIP) with body mass index (BMI)

Serum biomarkers of lipids		Normal Fundus No. (%)	HR changes No. (%)	Pearson Chi-square test (p value)
Total cholesterol level (mg/dl)	Normal	27 (8.5%)	3 (0.9%)	**0.01**
	Raised	256 (80.7)	31 (9.8%)	
Total Triglycerides level (mg/dl)	Normal	108 (34.0%)	10 (3.1%)	0.99
	Raised	175 (55.2%)	24 (7.6%)	
Total HDL level (mg/dl)	Normal	99 (31.2)	6 (1.9%)	4.1
	Low	184 (58.0%)	28 (8.8)	
Total LDL level (mg/dl)	Normal	239 (75.3%)	32 (10.1%)	2.28
	Raised	44 (13.9%)	2 (.6%)	
Atherogenic index of plasma	**Body mass index (BMI)**			
	Risk category	Normal No. (%)	Raised BMI **(>25)** No. (%)	p-value
	Low risk	2 (.6%)	2 (.6%)	0.71
	Intermediate risk	5 (1.6%)	2 (.6%)	
	High risk	172 (54.2%)	134 (42.2%)	

where they found a significant association of AIP with BMI in postmenopausal ladies. This could be due to the fact that our study subjects had a mean BMI which was just about normal, in addition, postmenopausal ladies are more likely to have higher BMI due to pregnancy-related factors and dietary habits.

This study further emphasized a fact that routine Ophthalmological checkup of hypertensive patients is a must; particularly in view of the high prevalence of hypertension in our setting. In patients having signs of HR further evaluation of cardiovascular risk factors including a lipid profile is also warranted as early identification and treatment of these risk factors may be helpful in preventing blindness as well as cardiovascular morbidity and mortality. The atherogenic index of plasma (AIP) can be a helpful biomarker to predict future cardiac morbidities especially in patients with hypertensive retinopathy.

CONCLUSION

The prevalence of hypertensive retinopathy was low in this study when compared with national and international studies. This study could conclude that, if the serum biomarkers of lipids including an atherogenic index of plasma are routinely examined and kept within normal range, the target organ damage due to hypertension can be reduced including hypertensive retinopathy. Electrocardiograms changes can occur silently in hypertensive patients. The atherogenic index of plasma should be used as a predictive risk factor for future cardiac events in hypertensive patients.

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