Original Research Article

# Study of association between fundus changes and serum lipid profile in patients of essential hypertension

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## Abstract

**Background**: To evaluate the role of dyslipidemia on fundus changes in hypertensive patients,and to correlate above findings with the components of lipid profile (LDL, HDL, VLDL, Total cholesterol and triglycerides). **Method**: One hundred consecutive subjects who attended ophthalmology OPD and inpatients of A.J Institute of Medical Sciences Mangalore who were diagnosed with primary essential hypertension were enrolled in this prospective study. All the subjects (200 eyes) were subjected to a detailed ophthalmic examination. Fundus changes were classified according to Keith, Wagener and Barker (KWB), and Modified Scheie's grading system. Investigations in this study include Complete blood count (Hb, TLC, DLC, ESR), Urine routine and microscopic examination, random blood sugar, fasting serum lipid profile. Other investigations like blood urea, serum creatinine, Chest X-ray, ECG, ECHO, CT scan were done based on clinical diagnosis and suspicion of end organ dysfunctions. Data were collected using apre-structured proforma and analysed using SPSS 13.0 **Results**: Out of the 100 patients with essential hypertension, 75(75%) had retinopathy and the remaining 25(25%) subjects had no retinopathy. Severity of hypertension correlated well with severity of retinopathy ($p<0.008$). No sex preponderance towards developing retinopathy was found in this study ($p<0.544$). Our study showed significant relationship between various grades of retinopathy and duration of hypertension ($p<0.000$). A positive correlation of hypertensive retinopathy was found with total cholesterol value ($p<0.013$), serum triglycerides ($p<0.039$) and cholesterol:high-density lipoprotein (cholesterol:HDL) ratio ($p<0.015$). **Conclusion:** This study proved a definite association between serum lipid parameters and the prevalence of hypertensive retinopathy (HR).

**Keywords:** Cholesterol, Dyslipidemia, High-density lipoprotein, Hypertensive retinopathy.



## Introduction

Hypertension (HT) that affects 50 million people in the United States and approximately one billion worldwide is a silent killer [1-5]. Therefore, to ensure a safe diagnosis of end organ damage linked to HT before it becomes symptomatic, the role of optimizing risk stratification strategies is important. The retina provides a window to study human circulation. Retinal arteries can be quickly and noninvasively visualized and share common anatomical and physiological features with cerebral and coronary microcirculation [6-9]. HT affects multiple organ systems (kidney, retina, heart and brain). In the vascular beds of hypertensive patients,inflammatory pathways take a significant part [10]. HR is one of the essential HT vascular complications. Automotive retinal circulation management fails with elevated blood pressure above vital levels. The level of retinopathy is not entirely taken into account by elevated blood pressure alone. Other causes potentially participate in the pathogenesis of HR, along with the influence of high blood pressure [11]. Several tests have shown that serum and plasma total cholesterol concentrations have been strongly and positively associated with coronal artery atherosclerosis,spreading through a broad spectrum of total cholesterol levels and LDL cholesterol [12,13]. Hyperlipidemia is considered to be a significant risk factor in patients with hypertension [14].Dyslipidemia itself is considered to be a retinopathy and other ocular abnormality risk factor. HTis difficult when associated with conditions such as diabetes. Its function in combination with diabetes retinopathy and maculopathy linked to age has been well established [15-17].Dyslipidemia may serve as a predisposing factor, an aggravating or complicating factor in hypertensive patients. An understanding of various ocular manifestations, spectrum of findings and their association with components of lipid profile (LDL, HDL, VLDL, Total Cholesterol, and Triglycerides) may be helpful in risk stratification and in tailoring of anti-hypertensive and lipid lowering treatment.

In view of this, the current study aimed to evaluate the role of dyslipidemia on fundus changes in hypertensive patients, and to correlate above findings with the components of lipid profile (LDL, HDL, VLDL, Total cholesterol and triglycerides).

**Method**

This was a prospective study carried out in the Ophthalmology department of a Medical college in South India for a period of one year. A pre-structured proforma was utilized for data entry. One hundred consecutive subjects who were diagnosed with primary essential HT were enrolled in this study. All the subjects (200 eyes) were subjected to a detailed ophthalmological examination. Fundus changes were classified according to Keith, Wagener and Barker (KWB), and Modified Scheie's grading system. Investigations in this study include Complete blood count (Hb, TLC, DLC, ESR), Urine routine and microscopic examination,Random blood sugar, Fasting serum lipid profile. Other investigations like blood urea, serum creatinine, Chest X-ray, ECG, ECHO, CT scan were done based on clinical diagnosis and suspicion of end organ dysfunctions. Visual fields(Humphreys Field analysis)done if required. The normotensive patients, patients suffering from diabetes and other systemic diseases, patients with high myopia, and patients with hazy ocular media in

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both the eyes and other retinal vascular disorders were excluded from the study. For all the study patients included in this study, the detailed hypertensive status (age of onset, duration of thedisease, associated conditions like diabetes, renal, cardiovascular, cerebrovascular disease, any medications (antihypertensive drugs, lipid lowering drugs), family history, other risk factors like smoking, alcohol, tobacco use were recorded), detailed ophthalmic examination of the patient(best corrected visual acuity, refraction, slit lamp examination of anterior segment, after anterior segment examination pupils were dilated with tropicamide eye drops, dilated fundus evaluation with direct ophthalmoscope, indirect ophthalmoscope, slit lamp biomicroscopy using 90D or78D lens). The fundus findings after dilated fundus examination were recorded in amsler chart and staging of HR was done using Modified Keith-Wagener-Barker Classification [17]. After complete evaluation patient was counselled and appropriate treatment was advised[18].

**Statistical analysis**

Statistical data analysis was done using SPSS Software version 13. The normality distribution was checked by D'Agostino's test. Categorical and numerical data was represented as frequencies (n) and proportions (%) and mean and standard deviation (SD), respectively. Demographic data (age, gender, grading of retinopathy, duration of HT, lipid profile distributions) were categorical data. Categorical data were analysed by Fisher exact test or chi square test ($x^2$) as appropriate. Comparision across grades of retinopathy with respect to various quantitative variables was done by ANOVA test. Spearman rank correlation test estimated the relationship between fundus retinopathy grade and lipid profile parameters. A p value of <0.05 was considered as significant.

**Result**

The following observations were made in our study:

**Table 1: Age and gender distribution**

| Age groups | Frequency | Percent |
|---|---|---|
| 21 – 40 | 18 | 18.0 |
| 41 – 60 | 61 | 61.0 |
| Above 60 | 21 | 21.0 |
| Total | 100 | 100.0 |
| **Gender** | | |
| Females | 45 | 45.0 |
| Males | 55 | 55.0 |
| Total | 100 | 100.0 |

The above Table 1 gives the age distribution across the 100 subjects. 18% subjects were between 21-40 years of age, 61% subjects were between 41 and 60 years of age, 21% subjects were above 60 years of age. In gender distribution across all the subjects were male to female ratio was 1.22:1 in this study.

**Table 2: Fundus retinopathy grade**

| Retinopathy grade | Frequency | Percent |
|---|---|---|
| Normal | 25 | 25.0 |
| Grade 1 | 22 | 22.0 |
| Grade 2 | 42 | 42.0 |
| Grade 3 and more | 11 | 11.0 |
| Total | 100 | 100.0 |

As shown in Table 2, out of 100 patients, 25 patients had normal fundus, 22 patients had grade 1 HR, 42 patients had grade 2 HR, 11 patients had grade 3 and grade 4 HR.

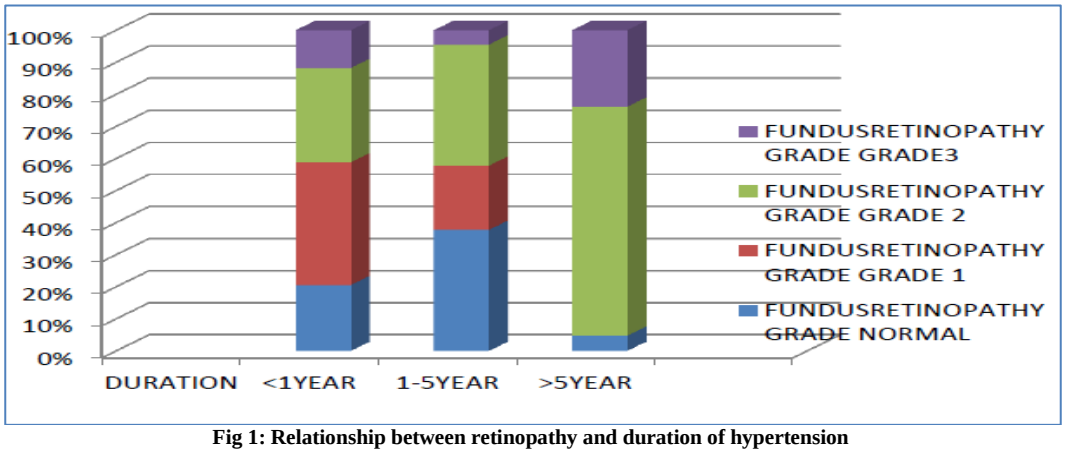


**Fig 1: Relationship between retinopathy and duration of hypertension**

As shown in Figure 1, out of 100 patients, 34(34%) patients had HT for less than 1 year duration. Of which 27(79.4%) had retinopathy of varying degrees, while 7(20.6%) had no retinopathy. There were 45(45%) patients who had HT for 1-5 years duration, of which 28(62.2%) patients had retinopathy, while 17(37.8%) patients had no retinopathy. Next group consists of 21(21%) patients with >5 years duration of HT, of which 20(95.2%) patients had retinopathy and 1(4.8%) patient had no retinopathy. The relationship between various grades of retinopathy and duration was statistically significant.

**Table 3: Relationship of Retinopathy with Serum Total Cholesterol and Triglycerides**

| Cholesterol (mg/dl) | Fundus Retinopathy Grade | | | | Total |
|---|---|---|---|---|---|
| | Normal | Grade 1 | Grade 2 | Grade 3 and more | |
| <200 mg/dl(within normal limits) | 22(35.5%) | 12(19.4%) | 23(37.1%) | 5(8.1%) | 62 (100%) |
| >200mg/dl(above normal limits) | 3(7.9%) | 10(26.3%) | 19 (50.0%) | 6(15.8%) | 38(100.0%) |
| Total | 25(25.0%) | 22 (22.0%) | 42 (42.0%) | 11 (11.0%) | 100(100.0%) |
| **Triglycerides(mg/dl)** | | | | | |
| <150 mg/dl(within normal limits) | 21(30.0%) | 18(25.7%) | 26 (37.1%) | 5(7.1%) | 70(100.0%) |
| >150mg/dl(above normal limits) | 4(13.3%) | 4(13.3%) | 16(53.3%) | 6(20.0%) | 30(100.0%) |
| Total | 25(25.0%) | 22 (22.0%) | 42 (42.0%) | 11(11.0%) | 100(100.0%) |

*Normal value of Total Cholesterol< 200mg/dl, Normal value of Triglycerides<150mg/dl

As shown in Table 3, out of 100 patients, 62 patients (62%) had Total cholesterol within normal limits, of which 40 patients (64.6%) had retinopathy and 22 patients (35.5%) had no retinopathy 38 patients (38%) had Total cholesterol above 200mg/dl of which 35 patients (92.1%) had retinopathy and 3 patients (7.9%) had no retinopathy Overall the increase in total serum cholesterol levels correlated well with increasing grade of retinopathy p<0.013 which is statistically significant.

Out of 100 patients 70 patients had triglycerides level within normal limits of which 49 patients (69.9%) had retinopathy and 21 patients (30%) had no retinopathy. 30 patients had triglyceride level of >150mg/dl, of which 26 patients (86.6%) had retinopathy and 4 patients (13.3%) had no retinopathy. Overall, serum triglycerides levels correlated positively with increasing severity of retinopathy which was statistically significant (p<0.039).

**Table 4: Relationship of retinopathy with serum HDL and LDL Cholesterol**

| Serum HDLcholesterol(mg/dl) | Fundus retinopathy grade | | | | Total |
|---|---|---|---|---|---|
| | Normal | Grade 1 | Grade 2 | Grade 3 and more | |
| <40 | 7(15.9%) | 10(22.7%) | 24(54.5%) | 3 (6.8%) | 44(100%) |
| 40-60 | 15(33.3%) | 9(20.0%) | 13(28.9%) | 8(17.8%) | 45(100.0%) |
| >60 | 3(27.3%) | 3(27.3%) | 5(45.5%) | 0(0%) | 11(100.0%) |
| Total | 25(25.0%) | 22 (22.0%) | 42 (42.0%) | 11(11.0%) | 100(100.0%) |
| **Serum LDLCholesterol (mg/dl)** | | | | | |
| <50 | 1(14.3%) | 0(0%) | 5(71.4%) | 1(14.3%) | 7(100.0%) |
| 50-100 | 7(29.2%) | 6(25.0%) | 8(33.3%) | 3(12.5%) | 24(100.0%) |
| >50 | 17(24.6%) | 16(23.2%) | 29(42.0%) | 7(10.1%) | 69(100.0%) |
| Total | 25(25.0%) | 22 (22.0%) | 42 (42.0%) | 11(11.0%) | 100(100.0%) |

*HDL normal value = 40-60mg/dl, LDL normal value = 50-100mg/dl

As shown in Table 4, Out of 100 patients 44 patients (44%) had HDL Cholesterol <40 mg/dl, of which 37 patients (84%) had retinopathy and 7 patients (15.9%) had no retinopathy 45 patients had HDL cholesterol level within normal limits (40-60mg/dl), of which 30 patients (66.7%) had retinopathy and 15 patients (33.3%) had no retinopathy 11 patients had HDL cholesterol level =>60mg/dl, of which 8 patients (72.8%) had retinopathy and 3 patients (27.3%) had no retinopathy. Overall there was no statistically significant relation between the serum levels of HDL-cholesterol and the grades of retinopathy (p<0.116).

Out of 100 patients studied 7 patients (7%) had LDL Cholesterol levels of <50mg/dl, of which 6 patients (85.7%) had retinopathy and 1 patient (14.3%) had no retinopathy. 24 patients had LDL Cholesterol levels between (50-100) mg/dl, of which 17 patients (70.8%) had retinopathy and 7 patients (29.2%) had no retinopathy. 69 patients (69%) had LDL Cholesterol levels of >100mg/dl of which 52 patients (75.3%) had retinopathy and 17 patients (24.6%) had no retinopathy. Overall there was no statistically significant relation between the serum levels of LDL Cholesterol and the grades of retinopathy (p<0.671).

**Table 5: Relationship of retinopathy with Cholesterol:HDL and LDL:HDLratio**

| Cholesterol:HDL(mg/dl) | Fundus Retinopathy Grade | | | | Total |
|---|---|---|---|---|---|
| | Normal | Grade 1 | Grade 2 | Grade 3 and more | |
| <2.5 | 7(63.6%) | 1(9.1%) | 3(27.3%) | 0(0%) | 11(100%) |
| 2.5-5 | 15(27.8%) | 12(20.0%) | 22(40.7%) | 5(9.3%) | 54(100.0%) |
| >5 | 3(8.6%) | 9(25.7%) | 17(48.6%) | 6(17.1%) | 35(100.0%) |
| Total | 25(25.0%) | 22 (22.0%) | 42 (42.0%) | 11(11%) | 100(100.0%) |
| **Serum LDL: HDL ratio(mg/dl)** | | | | | |
| 0-2 | 12(37.5%) | 5(15.6%) | 12(42.0%) | 3(9.4%) | 32(100.0%) |
| >2 | 13(19.1%) | 17(25.0%) | 30(44.1%) | 8(11.8%) | 68(100.0%) |
| Total | 25(25.0%) | 22 (22.0%) | 42 (42.0%) | 11(11%) | 100(100.0%) |

*Cholesterol:HDL normal value=2.5-5, LDL:HDL normal value=0-2 mg/dl

As shown in Table 5, Out of 100 patients 11 patients (11%) had Cholesterol:HDL ratio <2.5, of which 4 patients (36.4%) had retinopathy and 7 patients (63.6%) had no retinopathy. 54 patients had Cholesterol:HDL ratio within normal limits (2.5-5), of which 39 patients (72.2%) had retinopathy and 15 patients (27.8%) had no retinopathy. 35 patients had Cholesterol:HDL ratio >5, of which 32 patients (91.4%) patients had retinopathy and 3 patients (8.6%) had no retinopathy. Overall the increasing levels of Cholesterol:HDL ratio correlated positively with increasing severity of retinopathy, which was statistically significant (p<0.015).Out of 100 patients, 32 patients (32%) had LDL: HDL ratio of 0-2, of which 20 patients (62.5%) had retinopathy, while 12 patients (37.5%) had no retinopathy. The next group of 68 patients (68%) had serum LDL:HDL ratio >2, of which 55 patients (80.9%) had retinopathy,

whereas 13 patients (19.1%) had no retinopathy. Overall there was no statistically significant relation between the serum levels of LDL:HDL ratio and the grades of retinopathy (p<0.280).

**Discussion**

A prospective hospital research study for one year has been undertaken to assess the effect of dyslipidemia on fundus changes in hypertensive patients and to compare the results with the lipid profile components (LDL, HDL, VLDL, Total cholesterol and triglycerides). The research involved a total of 100 patients diagnosed with primary essential HT. They were categorized into retinopathy, and no retinopathy category initially, further retinopathy patients were divided into grade I, II, III and IV retinopathy based on the severity of retinopathy[19].

**Age and Sex Prevalence**

The mean age of patients in present study population was 50.85 ±11.41 years ranging from 21-73 years. Out of these 75 patients belonged to retinopathy group with mean age of 52.48±11.24years and 25 patients had normal fundus, with mean age of 46.12±11.82 years. According to Nguyen et al, retinal vasculature can be viewed directly and noninvasively, offering a unique andeasily accessible "window" to study the health and disease of the human microcirculation in vivo[20].In a study carried out by Bastola et al and Nguyen et al the mean age of the study group was 58.5years (SD=9.2 years; range=33-48), 56.50±21.00 years, range=35 to 78 years respectively [20,21]. Epidemiological trials have found that HR symptoms are normal even in those without ahistory of HT in people 40 or older. Prevalence with different symptoms of retinopathy ranged from 2 to 15%. There were 55 males and 45 females in our study group. Out of which 44(44%)males and 31(31%) females had retinopathy. 11(11%) males and 14(14%) females had no signs of retinopathy respectively, there was no significant sex preponderance (p<0.544). Variations in the prevalence of specific signs of HR according to age and sex have not been consistently demonstrated [22-24]. Fewer HR trials have been conducted. Two reports suggest that the prevalence of diverse retinopathy symptoms varies between 6 and 10 per cent over five to seven years [25,26]. However, study by Rasoulinejad revealed that smoking, dyslipidemia and gendershowed no association with retinopathy [27].

**Blood pressure**

A significant correlation in relation to severity of HT and retinopathy (p<0.008) was observed in our study.The relationship between various grades of retinopathy and duration of HT was statistically significant (p<0.000).Numerous tests have shown that retinopathy symptoms and high blood pressure are closely associated with [22-25,27]. The effect of high blood pressure history on the onset of complex retinal signs has been assessed by two studies. The current level, but not previous blood pressure levels is associated with other symptoms of focal arteriolar narrowing, retinal hemorrhage, microaneurysms, and cotton-wool spots may also indicate more seriousness of HT in recent times[28,29].

**Lipid Parameters**

Studies proved correlation between increased blood pressure and altered lipid profiles. One study demonstrated positive correlation between high cholesterol levels and blood pressure.Although the levels of serum low density lipoprotein in coronary artery disease are now understood to increase,relatively little is reported about whether in HR levels of serum lipoprotein are dramatically increased. New findings indicate that in hypertensive patients with fundus changes, serum lipidshave been statistically improved. The results were close to smaller sample analysis conducted in Nepal [30].HR signs are closely related, though not reliably, to an increase in blood pressure, serum lipids and other atherosclerosis risk factors [31]. However, this analysis found that the serum lipids in hypertensive patients with fundus changes were significantly increased. Serum cholesterol and serum lipids were elevated while free fatty acids were normal, relative to normalpeople with HT without retinopathy [32]. The free fatty acids, serum lipids and serum cholesterol in patients with HR have been increased relative to average people.

According to the study by Adhikari et al, the duration of hypertension was found to be strongly associated with development of hypertensive retinopathy. The increase in all the lipid profile parameters and the obesity were found to be strongly associated with retinopathy in hypertensive patients and the overall association of serum triglycerides with retinopathy was found significant(p<0.0001) [33]. Further to this observation, a longer duration of diabetes, poorer glycaemic and lipid control, and higher BP level were the main predictors of development of HR [34].

**In relation with Total serum cholesterol**

In our study increase in serum total cholesterol levels correlated well with increasing grades of retinopathy which was statistically significant (p<0.013). In a study done by Akshar V Soni in Kota increased incidence of HR was observed in patients having high serum total cholesterol level and this association was statistically significant (p<0.0001) [34]. In a study by Gupta et al, the disparity between the mean serum cholesterol level (p<0.001) of patients with normal fundus and those with varying degrees of HR has also been shown to be statistically significant[35]. In another study by Hanff et al also showed that there was an increased incidence of HR inpatients having high serum cholesterol level and this association was statistically significant(p<0.0008)[36]. Cuspidi described the prevalence of advanced retinal microvascular lesions andtheir associations with cardiac and extracardiac signs of target organ damage (TOD) in a large selected hypertensive population [37].

**In relation with serum Triglycerides**

Our study showed positive correlation of serum triglycerides levels with increasing severity of retinopathy and it was statistically significant (p<0.039).

Similar to observations by Gupta study, another study by Holmes et al (2018) reported similar association between serum triglycerides levels and HR changes which was statistically significant (p<0.01) [38]. Mean triglycerides levels were also found to be high in grade II and higher HR patients in a study carried out by Tada et al [39]. Another study proved that serum triglycerides were associated with first cardiovascular events among high-risk diabetes patients with hypercholesterolemia and retinopathy [40].

**In relation with serum HDL Cholesterol**

In our study the retinopathy group had mean HDL-Cholesterol valuesof 41.18 and 47.76for no retinopathy group. The serum HDL-cholesterol and retinopathy were not significantly linked.According to Gupta et al study mean serum HDL-cholesterol value for the retinopathy group was 38.68 and that for the no retinopathy group was 39 [20]. Bastola et al also showed similar findings [21]. In a study done by Akshar V Soni serum HDL-cholesterol values for retinopathy group were 42.70 and that for no retinopathy group was 43.61 [33]. Except the study by Karaca et al [41], no further research has shown that serum HDL cholesterol is correlated with HR until recently.

**In relation with serum LDL Cholesterol**

In our study there was no statistically significant relation between the serum levels of LDL cholesterol and the grades of retinopathy (p<0.671). This finding in our research contrasts with the findings of other researchers, where serum LDL cholesterol and retinopathy are significantly correlated. Gupta et al showed significant association between serum LDL-cholesterol and the severity of the retinopathy (p<0.01) [20]. Badhu et al and Bastola et al also showed a significant correlation between high serum LDL-cholesterol and HR [21,30]. In a study done in a medical college in Kota, they found a significant association between high serum LDL-Cholesterol and the severity of the retinopathy, (p<0.0001) [33].

**In relation with serum LDL:HDL cholesterol ratio**

In our study the association of LDL:HDL-Cholesterol ratio was not found to be statistically significant (p<0.280). In a study done by Gupta et al association of LDL:HDL-Cholesterol ratio was found to

be statistically significant (P<0.0001) [20]. No correlation of this kind has been reported so far in the literature. In this present study it wasfound that in people with grade 2 or higher grades of HR mean serum cholesterol level and mean triglyceride levels was substantially elevated.

However,the association between dyslipidemia and HR requires further studies to determine its role in pathogenesis and the impact of treatment of dyslipidemia on HR.Dyslipidemia has an important part in pathogenesis of HR. In view of the high prevalence, of HR in our setting, we can confidently conclude that regular ophthalmological checkup of hypertensive patients are a must. A routine lipid profile can reduce ocular morbidity in all hypertensive patients. One study assessed the association between hypertensive retinopathy in patients of essential hypertension with an altered serum lipid profile [42].

**Conclusion**

Our study reported increase in incidence of hypertensive retinopathy with increase of serum total cholesterol, and serum triglycerides. However, no correlation was found between LDL-cholesterol and HDL-cholesterol and hypertensive retinopathy.Dyslipidemia can be considered as important risk factor for not only the prevalence and severityof retinopathy but also for other end organ failure. Preservation of vision may be an additional motivating factor for lowering serum lipid levels in persons with hypertension in whom they are elevated.The clinical consequences of our results isa suggestion to ophthalmologists to check lipidparameters in patients with hypertensive retinopathy. Preservation of vision may be an additional motivating factor for lowering serum lipid levels in persons with hypertension in whom they are elevated.

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