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Biomarkers of Lipid Status and Metabolism in Retinal Hypertensive Disorder

Ecaterina Pavlovschi[1*], Djina Borovic[2], Valeriana Pantea[3], Leonid Lîsîi[1], Olga Tagadiuc[1]

[1]Department of Biochemistry and Clinical Biochemistry, Nicolae Testemitanu State University of Medicine and Pharmacy, Chişinău, Republic of Moldova
[2]Ovisus Medical Private Center, Chişinău, Republic of Moldova
[3]Laboratory of Biochemistry, Nicolae Testemitanu State University of Medicine and Pharmacy, Chişinău, Republic of Moldova
Email: *ecaterina.pavlovschi@usmf.md

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Abstract

Background. Hypertension (HTN) is a preventable risk factor for morbidity and mortality worldwide. Hypertensive retinopathy (HR), its ocular complication, is characterized by progressive metabolic disorders and structural damage of the retina. Lipids play an essential role in retina homeostasis, so an alteration of lipid metabolism specific for HTN may be of great significance in the development of hypertensive retinal injury. The study aimed to investigate the association between HR, traditional lipid biomarkers changes, and the atherogenic index, as well as to highlight a possible role of lipid metabolism markers in HR diagnosis and prognosis. **Methods.** A total of 90 hypertensive patients from the Republic of Moldova, admitted to the Ovisus Medical Center, Chisinau, Republic of Moldova, for a vision check and firstly diagnosed with HR were recruited in our study. The enrolment period is between February 2018 and December 2019. They were divided into three groups based on fundoscopy, using Keith-Wagner-Barker grading system of HR—GI: 36 patients; GII: 35 patients; GIII: 19 patients. The level of serum lipids: triglycerides, total cholesterol, LDL-Chol, and HDL-Chol was determined, followed by the calculation of the atherogenic index of plasma. Results are displayed as the median and interquartile range (IQR). Kolmogorov-Smirnov and Shapiro-Wilk normality tests were used, followed by Levene's homogeneity of variance test. The groups were compared using the non-parametric Kruskal-Wallis and Mann-Whitney tests. The Spearman correlation coefficient was calculated (SPSS 23.0): $p < 0.05$—statistically significant. **Results.** It was attested a statistically significant increase of serum total cholesterol levels between the groups as the HR advanced ($p = 0.017$). In paired group comparisons, the total cholesterol level in GII significantly enhanced compared to GI 5.63 (IQR 0.69) mM/L vs. 5.49 (IQR 0.51) mM/L, $p = 0.05$ and in GIII com-

pared to GI 5.76 (IQR 0.82) μM/L vs. 5.49 (IQR 0.51) mM/L, p = 0.04, showing a significant weak positive correlation with the degree of HR (r = 0.292**, p = 0.005). A resembled tendency to increase was highlighted also in serum TAG levels between groups (p = 0.061), with a significant weak and positive correlation with the degree of HR (r = 0.249*, p = 0.018). The results for HDL-Chol, LDL-Chol and atherogenic index were insignificant. **Conclusion.** The study revealed statistically conclusive changes associated with the HR degree of the TAG and total cholesterol levels and the absence of changes in plasma lipoprotein content—LDL-Chol and HDL-Chol. Extended research is mandatory to conclude the role of lipid metabolism in the advancement of HR and to ascertain the potential diagnostic importance of the presented lipid status changes.

Keywords

TAG, Total Cholesterol, LDL-Chol, HDL-Chol, Hypertensive Retinopathy

1. Introduction

The global burden of hypertension (HTN) exceeds 1.5 billion people, being at the same time, the most significant but preventable risk factor for disability or even death caused by cardiovascular diseases [1] [2] [3].

Both the structure and the function of the vasculature of the eye are affected by the continuous increase of blood pressure. During the time, the spectrum of clinical signs known as hypertensive retinopathy, a common manifestation of HTN, can be explained by a range of pathological biochemical changes [4] [5].

HR is divided into several stages as a result of acute or chronic increased blood pressure. As an initial generalized response called vasoconstrictive phase, retina vasospasm is observed with an augmented vasomotor tone, whose purpose is to initially control the optimal blood volume.

The persistence of HTN leads to the next phase of retinopathy, known as sclerotic, recognized by the intimal thickening, hyperplasia of the media wall, and hyaline degeneration. The narrowing of the retinal arterioles—with their wall opacification ("silver" or "copper wiring"), are remarked as clinical signs with a further compression of the venules (known as arteriovenous "incision" or "pinching") [4] [5].

A further enhancement in blood pressure, leads to the disruption in the blood-retinal barrier, passing the pathological changes to the next phase—"the exudative" one. Specific modifications may be observed, such as micro aneurysms, haemorrhages in the retina, "cotton-wool" spots, and hard exudates that appear due to smooth muscles and endothelial cells necrosis, accompanied by the exudation of blood and lipids and an ischemia of retinal nerve fiber layer. In severe cases with uncontrolled and prolonged HTN, it is noticed the optic disc swelling—equivalent with grade 4 of HR [4] [5].

Nowadays, there is strong evidence that signs of HR have a powerful correlation with blood pressure levels [6] [7] [8]. However, high blood pressure cannot be fully responsible for all pathological mechanisms that lead 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] [10] [11] [12]. This is also supported by the fact that signs of hypertensive retinopathy have been found in patients without any known history of hypertension, thus increasing the importance of routine monitoring by an ophthalmologist, which could potentially allow early diagnosis of not only retinopathy, but hypertension itself.

During the time, several classifications of HR were introduced, where the most spread and frequently used was the Keith-Wagener-Baker grading system. This specific classification has become simplified due to the difficult and complex differentiation of early degrees of retinopathy, such as 1 and 2. These difficulties motivated the researchers to look for other sensible diagnostic methods like digital retinal photography and imaging software. The hardest part considering these two diagnostic methods is in the requirement of specialized expensive equipment, computer software, and specially trained technicians [13] [14].

There are several fast-developing areas of research in the field of HR nowadays - the already mentioned digital retinal imaging that might digitally quantify the retinal signs which are sustained by the optics retinal cameras, the determination of retinal vessel oxygen saturation using the retinal oximeter, evaluation of the retinal blood flow using Doppler optical coherence tomography, etc. Another approach is genetic studies that may explain some biological mechanisms.

Nevertheless, there is a gap in the research of biochemical markers in hypertension-induced retinopathy, which can certainly provide additional valuable information about the state of the retinal vasculature or of the retina itself. The need for laboratory markers is substantiated by both by the relative simplicity of procedures and economic reasons, biochemical analysis being relatively cheap.

Of interest would be to analyze the serum lipid levels of patients with HR, since dyslipidemia is a decisive modifiable risk factor for HTN [15], and that lipids are of great importance for retina structure and function. A large amount of lipids is present both in retina nerve fibers, in their synaptic connections, and the photoreceptor structures (lipid-soluble pigments). The outer segment membranes of the photoreceptor cells contain extremely high levels of polyunsaturated fatty acids and are extremely labile to oxidation [16]. Lately, 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 investigate the association between hypertensive retinopathy (HR) and traditional lipid biomarkers plus atherogenic index of plasma, as well as to highlight a possible utility of lipid marker in the diagnosis of HR.

2. Material and Methods

2.1. Patient Selection

An analytical, observational study was done on a representative sample of patients with primary hypertension with HR, that came for a primary random check at Ovisus Ophthalmological Medical Center, during the period February 2018-December 2019 and at whom in the first time was established the diagnosis of HR, by an extensive ophthalmological consult, that included the ascertainty of visual acuity, autorefracto-keratometry, perimetry, anterior and fundus biomicroscopy, ultrasonography, tonometry, gonioscopy, optical coherence tomography (OCT) of the macular area and the papilla of the optic nerve.

The representative research group was calculated in the EpiInfo 7.2.2.6 Program, "StatCalc - Sample Size and Power" section for analytical, observational (cohort) study, taking in the consideration the fact that the frequency of hypertensive retinopathy according to new bibliographic sources on average is 17.0% [3].

Eligibility Criteria

The diagnosis of HR was validated at recruitment by patient's history, review of the medical records, and meticulous specific ophthalmological check. The inclusion criteria were: male or female aged 30 - 80 years with high values of BP and HR; patients who have signed the informed consent; Moreover, subject was included in the research only if a fasting state was declared

Patients on antihypertensive medication or any drug use were excluded from the study due to a potential effect on the results of the study, along with the persons with metabolic condition (diabetes, severe obesity), serious somatic comorbidities, renal and neurological pathologies. Also, were not included individuals with history or presence of ocular trauma, optic nerve atrophies of various causes and ocular associated diseases (glaucoma, diabetic retinopathy, acute and chronic inflammatory processes, uveitis), that can interfere with retinopathy evolvement. In this study, we have only included patients with full data set including serum markers.

2.2. Sample Collection

Venous blood samples (5 ml) were collected and centrifuged for 5 minutes at 3000 rpm for further testing. Serum samples were dispensed into Eppendorf microtubes and frozen (−40˚C) prior being tested.

The level of the following serum lipid markers was measured: triglyceride (TAG), total cholesterol (TC), LDL-Chol (low-density lipoprotein cholesterol), and HDL-Chol (High-density lipoprotein cholesterol), followed by the calculation of the atherogenic index of plasma.

2.3. Biochemical Analysis

In order to assess the researched markers were used commercially available standard kits, produced by DAC-SpectroMed, Republic of Moldova.

TAG was determined using GPO/PAP enzymatic colorimetric method, based on the procedure described by Bucolo G *et al.* and Fossati P. *et al.* [18] [19]. Total cholesterol level was assessed according to the method described by Naito *et al.* and Melattini F. *et al.* [20] [21]. Burstein M. *et al.* and Lopes-Virella M.F. *et al.* method was applied for HDL-Chol assay after the precipitation of chylomicrons, VLDL and LDL [22] [23]. For the assessment of LDL-Chol was used de Nauck M. *et al.* method [24].

Atherogenic index evaluation

The atherogenic index of plasma (AIP) was calculated using the following established formula:

$$AIP = \text{Log}\,(TAG/(HDL - Chol)); \text{ [17]}$$

TAG—triacylglyceride; HDL-Chol—High-density lipoprotein cholesterol;

AIP > 0.1 is considered abnormal for cardiovascular risk; [25]

2.4. Statistical Analysis

The data were analyzed using SPSS 23.0 Software. Was tested the null hypothesis that the mean values of analyzed parameters are the same across all three groups. The values of lipid status markers were presented as the median and interquartile range (IQR). Kolmogorov-Smirnov and Shapiro-Wilk normality tests were used to analyse data distribution. The homogeneity of variance was determined by Levene's test. The groups were compared using the non-parametric Kruskal-Wallis and Mann-Whitney tests. The Spearman correlation test was used to assess the relationship between HR, four lipid components and AIP. Differences were considered statistically significant if the two-tailed p value was 0.05 or less.

2.5. Ethical Considerations

The Research Ethics Committee of the Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova, approved the study (12.02.2018). All study participants signed a written informed consent prior to enrollment in the study.

3. Results

The demographic data of the study revealed that in the research were included 90 hypertensive patients after satisfying the selection criteria, of which 52 females (57.8%) and 38 males (42.2%). The mean age was 59.79 ± 12.29 years (age distribution: 38 - 88).

Subjects were stratified into three groups in accordance with the Keith-Wagner-Barker grading system for HR, following a fundus examination:

*group 1 (GI) - 36 patients (Ist grade of HR);

*group 2 (GII) - 35 patients (2nd grade of HR);

*group 3 (GIII) - 19 patients (3rd grade of HR).

Our study did not include patients with 4th grade of HR. This fact is explained by the lack of sufficient number of patients plus the presence of other comorbid-

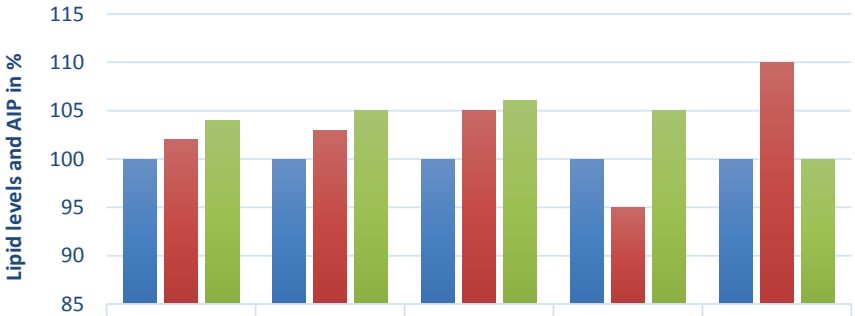
ities [2] [13].

A complete picture of the lipid status changes in serum samples of the hypertensive patients with different degree of HR are presented in Figure 1.

A tendency to enhance in parallel with HR escalation in grade (p = 0.061) was highlighted in serum TAG levels between groups.

In paired group comparisons, the TAG level in GII tend to increase in comparison to GI (+2%; 2.03 (IQR 0.18) mM/L vs. 2.07 (IQR 0.15) mM/L), and in GIII in comparison to GII (+2%; 2.10 (IQR 0.25) μM/L vs. 2.07 (IQR 0.15) mM/L) (Figure 2).

TAG levels demonstrated a statistically significant, weak positive correlation with the degree of HR (r = 0.249*, p = 0.018), as seen in Table 1.



	TAG (%)	Total cholesterol (%)	LDL-Chol (%)	HDL-Chol (%)	AI (%)
HR GI	100	100	100	100	100
HR GII	102	103	105	95	110
HR GIII	104	105	106	105	100

Figure 1. The changes in % of serum levels of lipids and atherogenic index of plasma in patients with different grade of HR.

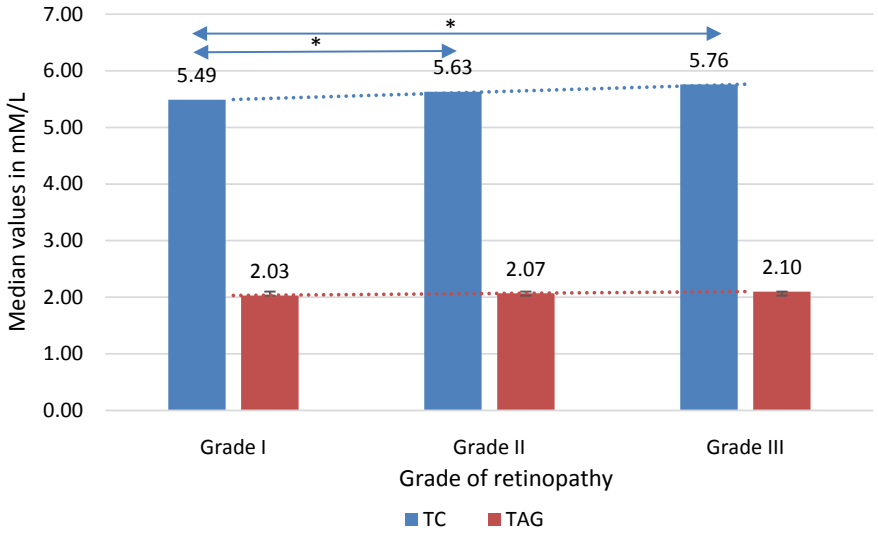


Figure 2. Serum TAG and total cholesterol levels in patients with different grade of HR. Note: differences between groups and p value: * < 0.05.

Table 1. Correlation of serum TAG, total cholesterol, LDL-Chol, HDL-Chol and AIP levels with HR grade.

		TAG	TC	LDL-Chol	HDL-Chol	AIP
Retinopathy	Correlation coefficient	0.249*	0.292**	0.129	0.084	0.108
	Statistical significance, 2-tailed (p)	0.018	0.005	0.225	0.429	0.312

Note: differences between groups and p value: * < 0.05; ** < 0.01.

A statistically significant change of serum total cholesterol levels between groups was attested, with a rise as the HR advanced (p = 0.017). In paired group comparisons, the total cholesterol levels in GII and GIII were significantly enhanced compared to GI: 5.63 (IQR 0.69) mM/L vs. 5.49 (IQR 0.51) mM/L, p = 0.05, and respectively, 5.76 (IQR 0.82) μM/L vs 5.49 (IQR 0.51), p = 0.04 (**Figure 2**).

The total cholesterol level showed a statistically significant (p = 0.005), weak positive correlation (r = 0.292**) with the degree of HR (**Table 1**).

Serum LDL-Chol showed insignificant correlation with the grade of HR (r = 0.129, p = 0.225) as HDL-Chol (**Table 1**) and statistically insignificant changes between groups (p = 0.302). In paired group comparisons, the serum LDL-Chol level in GII augmented compared to GI (+5%; 3.09 (IQR 0.37) mM/L vs. 2.94 (IQR 0.55) mM/L), and in GIII compared to GII (+1%; 3.13 (IQR 1.16) mM/L vs. 3.09 (IQR 0.37) mM/L) as seen in **Figure 3**.

There were not identified any correlations between serum HDL-Chol levels and retinopathy grade (r = 0.084, p = 0.429, **Table 1**).

Were asserted statistically insignificant changes of HDL-Chol levels between groups (p = 0.153) in serum, as the HR advanced in grade. HDL-Chol level in GII diminished compared to GI (−5%; 1.18 (IQR 0.20) mM/L vs. 1.24 (IQR 0.28) mM/L, p = 1.0), but with an ultimate increase in GIII compared to GII (+10%; 1.30 (IQR 0.36) mM/L vs. 1.18 (IQR 0.20) mM/L) (**Figure 3**).

Across all the participants, the mean of the AIP was 0.22 (IQR 0.10) in GI, with an insignificant enhancement in GII—+10%, 0.24 (IQR 0.06) and respectively decrease in GIII—−10%, 0.22 (IQR 0.11). There was no significant difference in the atherogenic index between groups (p = 0.146).

We systematically analyzed the associations between the total amounts of the researched markers of lipid status in the serum of patients with HR (**Table 2**).

As it is seen in **Table 2**, the study revealed a medium correlation coefficient between TC and TAG levels, TC and LDL-Chol levels, as well as between TC levels and HDL-Chol. A low positive and significant correlation was attested between TAG and HDL-Chol levels.

4. Discussion

It is well-known that HR is a multitarget pathology. Recent studies have demonstrated that the pathology of HR is clearly more complicated than simply high

Table 2. Correlations between TAG, total cholesterol, LDL-Chol and HDL-Chol levels in serum of patients with HR.

	TAG	TC	LDL-Chol	HDL-Chol
TAG	1.000	0.422***/p < 0.001	0.070/p = 0.513	0.240*/p = 0.023
TC	0.422***/p < 0.001	1.000	0.581***/p < 0.001	0.342***/p = 0.001
LDL-Chol	0.070/p = 0.513	0.581**/p < 0.001	1.000	−0.181/p = 0.087
HDL-Chol	0.240*/p = 0.023	0.342**/p = 0.001	−0.181/p = 0.087	1.000

Note: differences between groups and p value: * < 0.05; ** < 0.01; *** < 0.001.

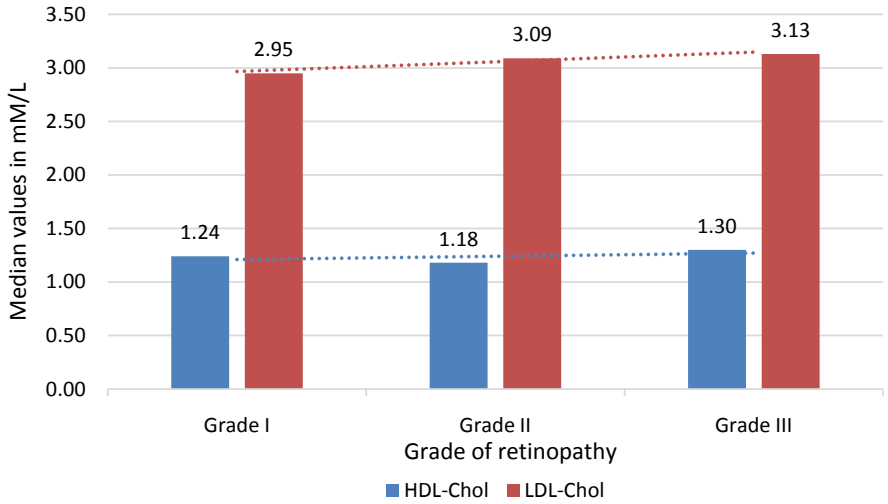


Figure 3. Serum changes of LDL-Chol and HDL-Chol levels in patients with different degree of HR.

blood pressure levels. Disorders of lipid metabolism can influence the HR evolution and even development. HTN and hyperlipidemia not only boost the development of atherogenesis but also lead to a series of degenerative alterations in the walls of medium- and large-sized arteries.

The results of our studies have shown a number of disorders in lipid status biomarkers in hypertensive damage of the retina. TAG and total cholesterol levels have shown a weak correlation with the grade of HR, changes remarked during time by other scientists, as it will be described later. These modifications can be explained by the fact that lipids play a role in development of HTN and its most common complications. Consequently, we may suggest involvement of lipids disorders in the development of HR, by endothelial dysfunction and breakdown of the blood retinal barrier that will favor serum lipids and lipoproteins exudation.

Enhanced lipid levels, seen as HR progressed, lead to the dysfunction of the vascular endothelium and subsequently to a reduced bioavailability of nitric oxide (NO). The peroxidation of lipids in lipoproteins in the vascular wall generate the local production of reactive carbonyl species that interfere with macrophages enrolment, the activation and proliferation of the cells, and ultimately

lead to chemical changes of vascular proteins, through advanced lipoxidation end products. As a result, all these processes will affect the structure and function of the vascular wall [17] [26].

The role of lipid metabolism markers in the progression of HR can be documented back to the 1975 when Singth *et al.* discussed for the first time the role of raised serum free fatty acids in precipitating HR [27].

Related studies with similar results as ours were performed during time. In 2012, Bastola *et al.* demonstrated a significant difference in the mean serum cholesterol level in all four stages of HR with a $p < 0.001$ [28]. And the result of our research also supports the findings of the study conducted by Gupta *et al.* (2013), that proved a positive correlation of HR with total cholesterol content ($p < 0.002$), with a gradual increase of the cholesterol level in parallel with the evolution in grade of HR [29].

Resembled outcomes with our study were remarked and regarding TAG. In the mentioned above Bastola *et al.* (2012) and Gupta *et al.* (2013) articles, was identified a statistically significant difference in mean triglyceride level for different degree of HR, highlighting their consequent augmentation through stages [28] [29]. Another research performed by Akhter *et al.* (2013) presented data that illustrated that increased serum cholesterol and serum triglyceride, were found to be significant risk indicators for developing retinopathy in the population [30]. The Hoorn study, performed by van Leiden *et al.* (2002), presented the fact that there are associations of lipid levels and blood pressure with retinopathy, which are stronger in individuals without diabetes than in individuals with diabetes [31].

Some studies have shown that LDL-Chol levels were significantly increased in individuals with HR of grade II or higher. According to a study by Badhu *et al.* (2003), elevated serum LDL-Chol was strong associated with HR ($p < 0.0196$) [32]. Moreover, previous results are supported by the van Leiden study (2002), which showed that retinopathy in people with hypertension without diabetes and hard exudates was associated with elevated serum LDL-Chol levels [31]. However, no other studies have attested any direct correlation between serum HDL-Chol or LDL-Chol and HR so far.

As for atherogenic index, in our study is higher than the recommended value of 0.1 and it is also seen an increase, even if insignificant, of its level as HR advanced in grade. The association of TAG and HDL-Chol reflects the equilibrium between risk and defensive/protective lipoprotein forces. So, the use of this index may be encouraged in order to detect the enhancement in probability of cardiovascular risk disease, as HTN with its complication [25].

However, data from some research papers are in a slightly dissonance with our results. As presented by Pai and Hegde (2019), there was no significant relationship between HR and serum lipids level. Their study has limitations, due to the fact that in the research were included only the individuals with grade I (84%) and grade II (16%) of HR. Still the data revealed an increase in total cholesterol, TAG and LDL-Chol levels and a decrease in HDL-Chol as HR pro-

gressed [15]. There are studies that have shown a positive correlation between LDL-Chol, HDL-Chol and HR [28] [32], however, this study just as the study by Gupta *et al.* [29] did not reveal a connection between them. Low HDL-Chol and high TAG levels induce an enhancement in small HDL particles, as well as an elevation in small, dense LDL-Chol particles [33].

Still, our study has several limitations, observed in the deviation of lipid status during progression of retinopathy, results that for sure cannot utterly be explained solely by HTN, HR or both of them concomitantly.

Our research included hypertensive patients that were not on any antihypertensive medication or any drugs that can influence the metabolism of lipids at that moment or also any other treatment that can doubt the outcomes.

On the other hand, a more meticulous approach is needed in order to be able to generalize the conclusions, being explained by the location of the research in one private hospital. It will be promising to expand research to a wider audience in various public hospitals and countries.

5. Conclusions

The impact of lipid metabolism disorders and blood lipid imbalances in the pathogenic mechanisms of the development of hypertension and its most common complications is well known. Still, there are not enough studies regarding the role of dyslipidemias in the development and progression of HR, and the existing ones are in many ways contradictory.

Our study revealed statistically conclusive changes associated with the HR degree of the TAG and total cholesterol levels and the absence of changes in plasma lipoprotein content—LDL-Chol and HDL-Chol, in patients included in the study. The results are partly consistent with the results of other researchers, but there were also differences compared to previous studies. This attests the need for further research with the extension of the sample, study groups and spectrum of markers to establish with certainty the role of dyslipidemia in the occurrence and progression of HR, as well as the possible diagnostic or prognostic value of lipid status markers. It is also important to determine the threshold values of the mentioned parameters, with their possible use in the patient stratification in groups and for a better grading system that will display the clinical features visualized on the retina fundoscopy.

Moreover, clinical and theoretical researches of the last years eliminated any hesitation regarding the fact that lipid metabolic changes play a significant role in the pathogenesis of HR. However, lipid-based treatment strategies are just beginning to rise up. An appropriate approach, for sure will assure the possibility of implementation of patient-based treatment with better outcomes.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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