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Original Article

Association between dyslipidemia and neovascular age-related macular degeneration: a case-control study

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Abstract: Objectives: Neovascular age-related macular degeneration (nAMD) is an advanced stage of AMD and is associated with an increased risk of visual impairment. Disturbances in lipid metabolism have been proposed as a major contributing factor to the pathogenesis of AMD. This study aims to investigate whether lipid profiles in the serum and components of dyslipidemia can be used as indicators for predicting progression to nAMD. Methods: A retrospective analysis was conducted involving 125 participants with nAMD. 125 non-AMD controls, matched by age, sex, and BMI, were incorporated into the study. The comparative analysis between the groups involved six lipid biomarkers in the serum: HDL-C, LDL-C TG, TC, ApoA1, and ApoB. Moreover, the existence of dyslipidemia and its constituents was assessed through t-tests, as well as univariate and multivariable logistic regression models. Results: Individuals with nAMD exhibited significantly higher serum HDL-C ($P = 0.02$) compared to the controls without AMD. Furthermore, the concentrations of ApoB were significantly less in the nAMD cohort ($P < 0.01$) when compared to the control group. During the investigation of the correlation between levels of serum HDL-C ($P < 0.01$) and serum ApoB ($P < 0.01$) with nAMD through logistic regression analysis, notable findings indicated a significant association between both variables and nAMD. However, by multivariate logistic regression analysis, neither serum HDL-C nor serum ApoB was an independent risk factor for nAMD. Conclusions: While individuals with nAMD demonstrated elevated serum HDL-C and reduced serum ApoB levels, these lipid markers may not be suitable as biomarkers for monitoring or preventing nAMD.

Keywords: Lipids, AMD, serum, dyslipidemia, biomarker

Introduction

Age-related macular degeneration (AMD), a prevalent condition among aging individuals globally, leads to permanent vision loss [1]. AMD can be categorized into three stages: early, intermediate, and late, with neovascular AMD (nAMD) being the advanced stage and the primary cause of severe vision loss [2, 3]. The two most widely utilized treatment modalities for nAMD are laser therapy and anti-vascular endothelial growth factor (anti-VEGF) therapy. Anti-VEGF therapy is the first-line treatment for nAMD, whereas laser therapy is effective only in specific subtypes of the condition. For instance, laser photocoagulation is applicable for treating macular neovascularization located outside the foveal center. In the case of the polypoidal choroidal vasculopathy subtype of nAMD, a combination of anti-VEGF therapy and photodynamic therapy can reduce the frequency of anti-VEGF treatments [4-6]. Although these therapeutic approaches can improve visual outcomes in certain nAMD patients, they are not curative and primarily serve to delay the onset of central vision loss [7]. Hence, a deeper understanding of the pathogenesis of nAMD is needed to identify novel targets and approaches intended for the prevention or deceleration of AMD progression to severe visual impairment.

AMD exhibits significant connections with lipid metabolism [8], particularly through genetic regulators of cholesterol transport. Genome-wide association studies (GWAS) have consistently implicated several important factors in lipoprotein metabolism, including Apolipoprotein E (APOE), Cholesterol Ester Transfer Protein (CETP), Adenosine Triphosphate-binding Cassette Transporter A1 (ABCA1), and Hepatic Lipase (LIPC) [9, 10]. Alterations in circulating

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levels of major lipoproteins - HDL-C, LDL-C, TG, and TC - have been documented in AMD patients, though these findings remain controversial [11, 12]. Current evidence presents conflicting perspectives: epidemiologic studies have identified associations between elevated HDL-C, LDL-C, and TG levels with increased AMD risk, while other reports have failed to confirm these associations or demonstrated inverse relationships [13-15]. Notably, emerging data suggest differential associations between serum lipid profiles and AMD subtypes. Furthermore, distinct pathogenic mechanisms may underlie the lipid-related risk patterns observed in nAMD versus geographic atrophy (GA) presentations [16, 17].

Dyslipidemia, defined as an abnormal lipid level in the blood, including elevated levels of TG, TC, LDL-C, or low HDL-C [18], is a widely recognized risk factor for cardiovascular disease (CVD) [19]. Numerous studies have suggested that dyslipidemia may also contribute to the development of AMD due to its shared vascular pathology with chorioretinal diseases [20]. Systematic reviews demonstrate a notable reduction in the likelihood of early AMD among individuals diagnosed with dyslipidemia who underwent treatment with statins [21]. Furthermore, patients with dry AMD have exhibited improved visual acuity when administered high-dose statin therapy [22]. However, the specific role of dyslipidemia in nAMD pathogenesis remains controversial.

The investigation aims to explore the connections between serum lipids, dyslipidemia, and nAMD, a complex disease. Biomarkers are crucial for identifying disease mechanisms, discovering new therapy targets, and monitoring disease progression, treatment effectiveness, and risk assessment. To tackle potential confounding factors, like age, sex, comorbidities, and body mass index, a case-control study will be conducted. The primary purpose is to examine whether serum lipids or dyslipidemia components serve as biomarkers for monitoring the occurrence of nAMD.

Materials and methods

Patients

Retrospective analysis of nAMD patients treated in our hospital from January 2021 to June 2023. A group of 125 patients diagnosed with nAMD were enlisted as the case group. The determination of nAMD diagnosis involved employing slit-lamp biomicroscopy, fluorescein angiography, indocyanine green angiography if deemed essential, and optical coherence tomography spectral domain (SD-OCT) imaging [23]. Inclusion criteria (applicable only to the nAMD group): Patients diagnosed with nAMD who have not received anti-VEGF treatment in the year before the start of this study. Exclusion criteria (applicable to all study subjects): the existence of any additional retinal or choroidal vascular issues, elevated nearsightedness, hypertensive-related retinopathy or choroidopathy, significant ocular injury, kidney ailment, liver ailment, autoimmune disorders, rheumatoid conditions, various forms of cancer, prolonged administration of lipid-lowering medications, and ongoing usage of thyroidal or glucocorticoid hormones. A matched control group of 125 participants without AMD history was recruited for comparison. A standard questionnaire was used to record medical history, lifestyle, and health-related behaviors at the beginning of the study. The collection of demographic and clinical data including age, gender, height, weight, BMI, and the presence of hypertension, diabetes, and coronary heart disease provided a comprehensive overview of the participants' health profiles. The sample was composed of 125 patients diagnosed with nAMD and an equal number of non-AMD controls. They did not significantly differ in age, gender, BMI, diabetes mellitus, coronary heart disease, or hypertension ($P > 0.05$) (**Table 1**).

Sample collection and testing

After fasting overnight for at least 8 hours, participants' blood samples were obtained. The freshly collected blood samples were analyzed biochemically within a maximum of four hours. Serum samples were utilized for the detection of TG, TC, HDL-C, LDL-C, and ApoA1/B by an AU5800 Biochemical Analyzer (Beckman Coulter, American). All operation procedures were strictly implemented following the instrument operation manual. The standard for dyslipidemia refers to the 2019 European Guidelines for the Management of Dyslipidemia, mainly Tables 3, 7, and chapter 5: Lipids and lipoproteins [24]. For specific values, see the notes of the table.

We compared the baseline demographic characteristics and blood lipid status of patients in the nAMD group and the control group, and incorporated any significant differences be-

Table 1. Baseline demographic characteristics in subjects with nAMD and control

Data	nAMD (n = 125)	Control (n = 125)	*P*-value
Age (years)	71.96±8.97	72.13±9.19	0.13
Gender (n)			0.23
Male	68	65	
Female	57	60	
Height (cm)	161.01±7.32	162.82±8.18	0.06
Weight (kg)	60.75±11.14	62.74±10.63	0.14
BMI (kg/m^2)	23.34±3.45	23.56±3.04	0.58
Diabetes Mellitus (n)	16	12	0.42
Coronary heart disease (n)	6	5	0.75
Hypertension (n)	58	70	0.13

nAMD, neovascular age-related macular degeneration; BMI, body mass index.

Table 2. Serum lipid profiles and prevalence of dyslipidemia in subjects with nAMD and control

Data	nAMD (n = 125)	Control (n = 125)	*P*-value
TG (mmol/L)	2.26±0.08	1.69±1.22	0.56
TC (mmol/L)	4.73±0.84	5.21±0.41	0.30
LDL-C (mmol/L)	2.61±0.67	2.78±0.77	0.07
HDL-C (mmol/L)	1.36±0.31	1.23±0.29	0.02
ApoA1 (mmol/L)	1.39±0.26	1.33±0.27	0.06
ApoB (mmol/L)	0.91±0.23	1.00±0.27	0.00
Dyslipidemia (n)	35	70	0.00
High TC (n)	11	23	0.03
High TG (n)	16	45	0.00
High LDL-C (n)	14	26	0.03
Low HDL-C (n)	6	12	0.14

ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; nAMD, neovascular age-related macular degeneration; Dyslipidemia was defined as the presence of any of the following: (1) high TC: TC ≥ 5.72 mmol/L; (2) high TG: TG ≥ 1.70 mmol/L; (3) high LDL-C: LDL-C ≥ 3.4 mmol/L; (4) low HDL-C: HDL-C < 0.91 mmol/L.

tween the groups into the logistic regression model. Based on the results of univariate and multivariate regression analysis, we identified the features related to nAMD.

Data analysis and statistics

We conducted a comprehensive analysis by comparing demographic characteristics, serum lipid profiles, apolipoproteins, and the presence of dyslipidemia among the nAMD cases and control groups. To achieve this, we used various statistical techniques and adjusted for potential confounders. To analyze continuous variables, we utilized the t-test, whereas, for categorical variables, chi-square tests were implemented. Additionally, we applied univariate and multivariable logistic regression models to explore the connections among demographic characteristics, lipid profiles, apolipoproteins, and various aspects of dyslipidemia with nAMD. To account for potential influences, we controlled for age, gender, BMI, diabetes mellitus, and hypertension in the multivariable logistic regression models. To evaluate the importance of group comparisons, we calculated odds ratios (ORs) by considering the normal control group as the baseline. An OR above 1 signifies that the variable functions as an autonomous risk factor for the study group, whereas an OR below 1 implies that the variable operates as an autonomous protective factor against the disease [16]. All statistical analyses were conducted utilizing SPSS statistical software (version 25, Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

Results

Serum lipids and components of dyslipidemia

There were no disparities observed in the levels of LDL-C, TG, and TC between the nAMD and control groups. The nAMD patients demonstrated a noticeably higher level of HDL-C ($P = 0.02$). In terms of dyslipidemia prevalence, there was a significantly lower occurrence of high TG ($P < 0.01$), high TC ($P = 0.03$), and high LDL-C levels ($P = 0.03$) in the nAMD cases compared to the non-AMD controls. The prevalence of low HDL-C ($P = 0.14$) did not display significant differences between the groups. Moreover, the nAMD cases exhibited a significantly lower concentration of ApoB when compared to the non-AMD controls ($P < 0.01$) (**Table 2**).

Table 3. Comparisons of the variables between nAMD and control groups by univariate logistic regression analysis

Data	OR	95% CI	*P*-value
Age	0.96	0.94-0.99	0.03
Gender	1.73	1.05-2.87	0.03
BMI	0.97	0.90-1.05	0.58
Diabetes Mellitus	0.72	0.32-1.59	0.42
Coronary heart disease	0.82	0.24-2.78	0.75
Hypertension	1.47	0.89-2.42	0.13
TC	0.85	0.64-1.12	0.25
TG	1.01	0.97-1.05	0.58
HDL-C	3.81	1.61-9.00	0.00
LDL-C	0.72	0.51-1.01	0.07
ApoA1	2.48	0.95-6.44	0.06
ApoB	0.23	0.08-0.65	0.00
Dyslipidemia	3.35	1.96-5.72	0.00
High TC	2.33	1.08-5.03	0.03
High TG	3.83	2.02-7.26	0.00
High LDL-C	1.37	1.21-1.90	0.20
Low HDL-C	2.10	0.76-5.80	0.15

ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; nAMD, neovascular age-related macular degeneration; Dyslipidemia was defined as the presence of any of the following: (1) high TC: TC ≥ 5.72 mmol/L; (2) high TG: TG ≥ 1.70 mmol/L; (3) high LDL-C: LDL-C ≥ 3.4 mmol/L; (4) low HDL-C: HDL-C < 0.91 mmol/L.

Factors contributing to the occurrence of nAMD

Age (P = 0.03), sex (P = 0.03), levels of serum HDL-C (P < 0.01), presence of dyslipidemia (P < 0.01), the occurrence of high TG levels (P < 0.01) and high TC levels (P = 0.03), as well as serum ApoB levels (P < 0.01), demonstrated significant associations with nAMD. Findings of the univariate logistic regression analysis are presented in **Table 3**.

Upon accounting for various factors such as age, gender, BMI, diabetes mellitus, and hypertension, the results indicated that the assessed serum lipids and dyslipidemia components did not function as independent risk factors for nAMD (P > 0.05). However, age (P < 0.01) and gender (P = 0.03) continued to display a significant association with the risk of nAMD. Findings of the multivariate logistic regression analysis are in **Table 4**.

Table 4. Comparisons of the variables between nAMD and control groups by multivariable logistic regression analysis

Data	OR	95% CI	*P*-value
Age	0.94	0.90-0.97	0.00
Gender	2.08	1.04-4.14	0.03
HDL-C	2.78	0.84-9.24	0.09
ApoB	0.326	0.07-1.43	0.13
Dyslipidemia	0.52	0.15-1.78	0.29
High TC	0.41	0.13-1.29	0.13
High TG	0.50	0.25-1.00	0.05

ApoB, Apolipoprotein B; HDL-C, high-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; nAMD, neovascular age-related macular degeneration; Dyslipidemia was defined as the presence of any of the following: (1) high TC: TC ≥ 5.72 mmol/L; (2) high TG: TG ≥ 1.70 mmol/L; (3) high LDL-C: LDL-C ≥ 3.4 mmol/L; (4) low HDL-C: HDL-C < 0.91 mmol/L.

Discussion

The prevention and management of advanced AMD and nAMD require the identification of biomarkers that can be easily monitored in individuals at risk. Evidence from genetic, biochemical, experimental, and clinical studies has established a compelling association between lipid dysregulation and AMD pathogenesis [25-27]. Dyslipidemia is associated with atherosclerosis and cardiovascular diseases. Monitoring lipoprotein levels in the blood has been a common practice in clinical settings for risk prediction and treatment monitoring of cardiovascular diseases [28]. Given the pathologic similarities between AMD and atherosclerotic CVD [20], this study investigated the relationship between serum lipid profiles and nAMD, with particular emphasis on evaluating dyslipidemia components as biomarkers for nAMD.

Our findings demonstrated a significant association between HDL-C levels and nAMD, with nAMD patients exhibiting elevated HDL-C concentrations compared to non-AMD controls. These observations are consistent with previous reports from observational studies and Mendelian randomization analyses [12, 14, 29-31]. While HDL-C is recognized for its cardioprotective properties [32, 33], paradoxically elevated levels may exert pro-oxidative and pro-inflammatory effects, contributing to impaired cholesterol homeostasis and glomerular accumulation, which could play a role in AMD development [34, 35]. However, our analy-

sis suggests that HDL-C does not independently predict nAMD risk, possibly due to the complex interplay of HDL-C-related genetic pathways. Notably, genetic polymorphisms in CETP and LIPC genes appear to mediate the relationship between HDL-C and nAMD [12]. Additional investigations into the function of HDL in nAMD may yield significant findings regarding the advancement of the disease, techniques to alter the risk of AMD, and new therapies.

Previous investigations propose that increased levels of blood lipids tend to protect against early-stage AMD, but not advanced-stage AMD [14, 30, 36]. A recent Mendelian randomization study has revealed an association between higher LDL-C and TG levels and a reduced risk of advanced AMD [12]. However, further analysis based on AMD subtypes showed that the protective effect of elevated levels of LDL-C and TG is only evident in intermediate and GA subtypes, but not in nAMD [12]. Our findings align with these observations, showing no substantial correlation between blood lipid levels and nAMD. This discrepancy may reflect distinct pathogenic mechanisms between GA and nAMD subtypes, as LDL-C and TG primarily influence drusen formation throughout GA progression [37], with minimal effect on angiogenic processes.

ApoB, especially ApoB-100, is an important apolipoprotein in LDL-C, and cell recognition and uptake of LDL are mainly achieved through the recognition of ApoB. Compared to LDL-C, ApoB level is more indicative of the incidence of cardiovascular disease [38]. Our study identified a significant correlation between ApoB levels and nAMD incidence, suggesting a link between nAMD pathogenesis and impaired lipid transport mechanisms. However, ApoB did not emerge as an independent predictor of nAMD, likely due to its complex hepatic biosynthesis and regulation by multiple metabolic factors.

Although there is an established link between AMD and CVD, the association between dyslipidemia and AMD, as revealed in this investigation, differs from that of CVD. Dyslipidemia is a well-recognized independent predictor of CVD, thus emphasizing the importance of dyslipidemia prevention and control in reducing CVD risk [39, 40]. However, findings from the current study indicate that the presence of dyslipidemia is lower in nAMD patients compared to non-AMD controls. Specifically, components of dyslipidemia such as elevated TG, TC, and LDL-C levels were less frequently observed in nAMD patients than in controls. These results suggest that the underlying pathogenesis of these two diseases may not be the same. Remarkably, a previous study also found no clear association between dyslipidemia and the presence of AMD [41]. Supporting the hypothesis that systemic inflammation induced by dyslipidemia may not significantly contribute to nAMD pathogenesis. This finding implies that the inflammatory cascade associated with dyslipidemia might not reach sufficient intensity to substantially influence nAMD development.

Several limitations should be acknowledged in this study. The results may be weakened due to the small sample size. This study's observational design hinders the establishment of a cause-effect association between lipid metabolism and nAMD. Despite adjustment for various factors by both univariate and multivariable analyses, the presence of residual or unmeasured confounders cannot be eliminated in any observational investigation. Therefore, it is necessary to conduct additional longitudinal follow-up studies on substantial cohorts to obtain a deeper understanding of the causal connection and the underlying pathologic mechanisms linking dyslipidemia and nAMD.

Conclusion

Our study identified significant associations between elevated serum HDL-C levels, decreased ApoB concentrations, and nAMD. However, neither parameter emerged as an independent risk factor for nAMD, suggesting limited utility as biomarkers for nAMD monitoring, prevention, or therapeutic intervention. These observations imply the existence of distinct regulatory mechanisms in lipid metabolism that may be associated with specific AMD phenotypes. Further comprehensive investigations are warranted to elucidate the complex pathophysiologic mechanisms underlying nAMD development and progression.

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This study has obtained the informed consent of enrolled patients.

Disclosure of conflict of interest

None.

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