Lipids in Health and Disease

RESEARCH Open Access

Serum lipid and lipoprotein profiles and their association with intraocular pressure in primary open-angle glaucoma: an observational cross-sectional study in the Chinese population

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Abstract

Background Glaucoma is a leading cause of vision impairment and permanent blindness. Primary open-angle glaucoma (POAG) is a prominent type of primary glaucoma; however, its cause is difficult to determine. This study aimed to analyze the serum lipid profile of Chinese POAG patients and assess its correlation with intraocular pressure (IOP).

Methods The study included 1,139, 1,248, and 356 Chinese individuals with POAG, primary angle closure glaucoma (PACG), and controls, respectively. Peripheral whole blood samples were collected at the time of diagnosis. Enzymatic colorimetry was used to determine serum levels of different lipids: high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides, cholesterol, and very low-density lipoproteins (VLDL). Additionally, immunoturbidimetry was used to quantify serum levels of apolipoproteins A (APOA), B (APOB), E (APOE), and lipoprotein A [Lp(a)], while intraocular pressure (IOP) was measured in all patients with POAG.

Results After adjusting for age and sex, patients with POAG exhibited elevated serum levels of VLDL, APOA, and APOE but mitigated cholesterol levels compared with the control participants. Significantly lower serum triglyceride, VLDL, and Lp(a) levels were found in patients with PACG than in control participants. Serum cholesterol ($P=0.019$; β = -0.75, 95% confidence interval [CI]: -1.38 – -0.12) and HDL levels ($P<0.001$; β = -2.91, 95% CI: -4.58 – -1.25) were inversely linked to IOP in patients with POAG, after adjusting for age, sex, and ocular metrics. In addition, serum Lp(a) levels were correlated with the average IOP ($P=0.023$; β = -0.0039, 95% CI: -0.0073 – -0.006) and night peak ($P=0.027$; β = -0.0061, 95% CI: -0.0113 – -0.0008) in patients with POAG.

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Conclusions Significantly different serum lipid and lipoprotein profiles were observed in POAG and PACG patients. This study highlighted the differences in serum lipid and lipoprotein levels among Chinese POAG patients and their relationship with IOP and IOP fluctuation. Serum lipid and lipoprotein profiles should be considered while evaluating glaucoma risk.

Keywords POAG, Serum lipid profile, Lipoproteins, Intraocular pressure

Background

Glaucoma, affecting nearly 80 million people worldwide, is a leading cause of blindness [1]. Primary open-angle glaucoma (POAG) is a common form with an unknown cause. Current therapeutic strategies for POAG primarily focus on reducing intraocular pressure (IOP), a well-recognized and modifiable risk factor [2], particularly in patients with high-tension glaucoma (HTG). However, a significant percentage of POAG patients exhibit IOP measurements that fall within the normal range (≤21 mmHg), categorized as experiencing normal tension glaucoma (NTG). Apart from the elevated IOP, older age [3], sex [4], ethnicity, positive family history, and high myopia [5] have been suggested as POAG risk factors. Nevertheless, its pathogenesis remains unknown. Exploring the mechanisms of disease could facilitate the development of novel treatment regimens.

In a prior genome-wide association study (GWAS), the Chinese population demonstrated a significant link between a variation in the ATP-binding cassette subfamily A1 (ABCA1) gene and POAG [6]. Recent outcomes offer additional proof that ABCA1 modulates the caveolin-1 (CAV1)/endothelial nitric oxide synthase/nitric oxide pathway, which in turn affects IOP [7]. Additionally, previous reports have suggested a connection between POAG in the Chinese population and variations in apolipoprotein E (APOE) levels [8, 9].

Based on the involvement of ABCA1, CAV1, and APOE in cellular cholesterol transport [10–12], it was hypothesized that lipid levels might be associated with POAG. Therefore, this investigation aimed to delineate the serum lipid profiles and levels of lipoproteins in Chinese POAG patients and compare them with those of primary angle-closure glaucoma (PACG) patients and normal controls. Researchers have investigated the connection between serum lipid and lipoprotein levels and IOP in POAG patients and further assessed the correlation between these levels and 24-hour IOP measurements.

Methods

Participants

A total of 1,139 Chinese individuals with POAG, 1,248 with PACG, and 356 control participants were enrolled at the Eye and Ear Nose Throat Hospital, Shanghai Medical College, Fudan University, Shanghai, China, between January 2015 and September 2021. The criteria used to identify individuals with POAG [13] were as follows: (1) Identification of open angles during a gonioscopy examination. (2) Indications of optic nerve impairment linked to glaucoma, distinguished by the existence of at minimum two of these attributes: a cup/disc ratio ≥ 0.6, asymmetry of cup/disc > 0.2 between the eyes, thinning of the neuroretinal rim either throughout or in specific areas, the existence of disc hemorrhage, and defects in the nerve fiber layer. (3) The visual field outcomes on OCTOPUS 101 automated perimetry were considered abnormal if there was one spot with a hindrance in sensitivity of 10 dB, two adjacent spots with a decline in sensitivity of 5 dB, or three adjacent spots with a hindrance in sensitivity of 2 dB. These outcomes were obtained during consistent and replicable visual field tests (with a reliability factor of < 15%). Patients with POAG were allocated into two groups, HTG and NTG, according to the highest recorded IOP measurement before therapy. In individuals with NTG, the greatest IOP measurement was ≤21 mmHg, while in patients with HTG, the IOP was >21 mmHg. PACG was detected in eyes exhibiting narrow angles, characterized by the presence of the pigmented portion of the trabecular meshwork being enclosed by a minimum of 180° of angle closure. This diagnosis applies to all angle closure instances, including synechial, appositional, segmental, and continuous types. It is also used when there is a significant amount of peripheral anterior synechiae that cannot be adequately treated by laser peripheral iridotomy. Additionally, the diagnosis necessitates an elevated IOP of >21 mmHg, as well as evidence of optic nerve damage characteristic of glaucoma, accompanied by associated visual field abnormalities. The criteria for excluding subjects with POAG and PACG included secondary glaucoma, other ocular conditions that may impact vision acuity or the visual field, history of intraocular surgery within 2 months prior to enrollment, history of ocular trauma, and systemic diseases encompassing familial hyperlipidemia, acute infection, metabolic syndrome, autoimmune diseases, or cancer [14]. None of the participants were taking lipid-lowering medications at the time of enrollment, according to the medical records. The control participants were recruited sequentially from among subjects who took part in annual health tests during the research period and were diagnosed with no eye diseases, except mild cataracts and had no history of intraocular surgeries or systemic diseases.

This study was approved by the Medical Ethics Committee of the Eye and Ear Nose Throat Hospital, Fudan University and adhered to the Helsinki Declaration (KJ2011-04).

Written informed consent was acquired from each volunteer following a comprehensive description of the study's objectives and possible consequences.

Ophthalmic and medical examinations

All research participants underwent comprehensive ophthalmic examinations, which included IOP measurement, slit-lamp examinations, and fundus examination. Visual field testing (OCTOPUS 101 automated perimetry) was performed on all patients with POAG, and visual field distortion was assessed using the mean deviation method. According to the clinical routine, 24-hour IOP measurement was only required for patients diagnosed with NTG and certain POAG patients who were suspected of having high night IOPs, based on the judgment of the attending doctors. Furthermore, the decision to perform a 24-hour IOP measurement was also related to accessibility. Some patients might have declined the procedure because of their poor physical or economic conditions. Therefore, only 269 patients in this cohort underwent 24-hour IOP measurement. This measurement was performed using a non-contact tonometer (NIDEK, Japan) before receiving any therapy. The IOP measurements were consistently conducted by a proficient operator. The IOPs of both eyes were monitored at regular intervals during the day and night with measurements taken every 2 h: at 8:00, 10:00, 12:00, 14:00, 16:00, and 18:00, during the daytime phase, and at 20:00, 22:00, 0:00, 2:00, 4:00, and 6:00 during the nocturnal phase. The patients engaged in typical indoor activities throughout the day and retired to bed at 10:00 PM. They were awakened every 2 h, and their IOPs were immediately monitored while seated from midnight to 6:00 AM. At each time point, three measurements were performed for each eye. Data were analyzed from the eyes with the most pronounced visual field impairment. The IOP fluctuation was ascertained by subtracting the lowest recorded IOP (trough IOP) from the highest recorded IOP (peak IOP) utilizing data from the 12 IOP measurements taken over 24 h. Day peak and night peak were respectively ascertained by the highest recorded IOP during the daytime (8:00 to 18:00) and nocturnal (20:00 to 6:00) phases. Comprehensive medical evaluations were conducted on all patients, including electrocardiography, plain radiography, assessments of liver function, renal function, infectious illness, blood pressure, heart rate, body temperature, height, and body weight. Face-to-face interviews were performed to obtain information on diabetes, hypertension, and other systemic diseases.

Serum lipid profile and lipoprotein measurement

In both patients and controls, serum lipid and lipoprotein levels were assessed. Briefly, blood specimens were obtained from each subject in the morning after an 8-hour fasting upon initial diagnosis of POAG at the glaucoma service. Blood tubes were centrifuged for 10 min at 3,000 rpm. Enzymatic colorimetry (Roche Cobas 8000C702, Mannheim, Germany) was used to assess the serum levels of high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), triglycerides, and cholesterol. Immunoturbidimetry (Roche Cobas 8000C702, Mannheim, Germany) was employed to assess the serum levels of apolipoproteins A (APOA), B (APOB), E (APOE), and lipoprotein A [Lp(a)]. To guarantee the precision of the detection system, a daily quality control test was conducted using a biochemical analyzer to assess the indoor air quality. Indoor quality control is carried out before specimen testing every day. The standard quality control products were purchased from the Shanghai Clinical Laboratory Center. The quality control level was restored to room temperature from −20 °C and tested on Roche Cobas C702 on the machine. The test results are compared with the concentration indicated on the quality control sample. If the concentration deviation is within one standard deviation (SD) range, it is considered qualified for quality control, and clinical specimen testing can be conducted. The monthly coefficient of variation was carefully controlled to remain between 3 and 5%.

Statistical analysis

The measurement results were reported as the average value ± SD. Multivariate linear regressions were implemented to compare the mean values of serum lipid and lipoprotein levels in different groups and to analyze the associations between IOP levels, including various 24-hour IOP levels, and serum lipids in patients with POAG. The connection between POAG and blood lipid and lipoprotein levels in Fig. 1 was ascertained with a multivariate logistic regression study. Age and sex are common confounding factors, which are also potential influencing factors of both blood lipid level and POAG disease. Furthermore, previous studies demonstrated that axial length was an essential element involved in 24-h IOP fluctuation in POAG patients, and central corneal thickness (CCT) was associated with IOPs [13]. Thus, age, sex, axial length, and CCT were adjusted as potential confounding factors in the multivariable linear regression studies. The beta coefficients with 95% confidence intervals (CI) were ascertained. The distribution normality of the residuals of each multivariate linear regression model was tested using the Kolmogorov-Smirnov test. The significance level was deemed at $P<0.05$. Bonferroni

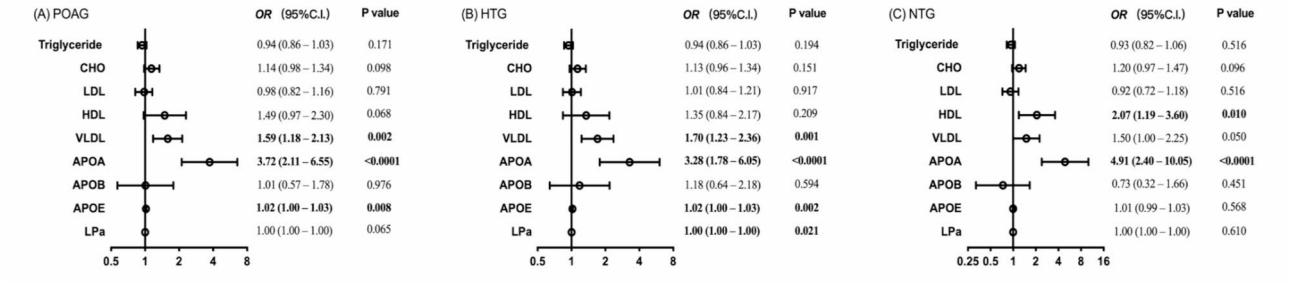

Fig. 1 Forest plots of risk for Primary Open-Angle Glaucoma (POAG), High-Tension Glaucoma (HTG), and Normal Tension Glaucoma (NTG) linked to serum lipid levels. Error bars show 95% confidence intervals (CI); *P*-values adjusted for age and sex, with bold indicating $P < 0.05$. Multivariate logistic regression analyzed POAG and blood lipid levels

Table 1 Demographic information of the study patients

	Control	Primary open-angle glaucoma	High-tension glaucoma	Normal tension glaucoma	Primary angle-closure glaucoma
Total number	356	1139	865	274	1248
Male	139 (39.04%)	748 (65.67%)	581 (67.17%)	167 (60.95%)	439 (35.18%)
Female	217 (60.96%)	391 (34.33%)	284 (32.83%)	107 (39.05%)	809 (64.82%)
Age (years)	67.75 ± 8.94	49.19 ± 16.04	47.94 ± 16.01	53.17 ± 15.52	63.76 ± 10.07
Intraocular pressure (mmHg)	16.12 ± 3.54	24.75 ± 7.95	26.27 ± 7.71	16.85 ± 2.91	/
Mean deviation (dB)	/	18.84 ± 7.80	18.84 ± 8.13	15.10 ± 7.81	/

correction was applied for several comparisons, and $\alpha' = 0.05/9$ (0.0056). Statistical analyses were conducted with R version 4.0.1 (http://www.rproject.org).

Results

Demographics of the study patients

Typically, 2,743 participants were recruited, comprising 1,139 POAG patients, 1,248 PACG patients, and 356 control subjects (Table 1). POAG patients had a significantly lower average age (49.2 ± 16.0 years) than control participants (67.8 ± 8.9 years) and PACG patients (63.8 ± 10.1 years) ($P < 0.001$). Male individuals constituted a significantly greater percentage (65.7%) of the POAG group than the control (39.0%; $P < 0.001$) and PACG group (35.2%; $P < 0.001$). The POAG cohort was allocated into two groups according to the highest IOP: the HTG group ($n = 865$) and the NTG group ($n = 274$). The sex ratio between the HTG (male/female = 2.05) and NTG groups (male/female = 1.56, $P = 0.059$) did not have a significant variation. However, the mean age of the HTG group (47.9 ± 16.0 years) was significantly lower than that of the NTG participants (53.2 ± 15.5 years; $P < 0.001$).

Serum lipid and lipoprotein levels in POAG, PACG, and control participants

POAG patients exhibited significantly lower serum cholesterol levels (4.60 ± 0.91 mmol/L vs. 4.66 ± 0.95 mmol/L, $P = 0.043$) but higher VLDL (1.28 ± 0.66 mmol/L vs. 1.06 ± 0.60 mmol/L, $P < 0.001$), APOA (1.46 ± 0.39 g/L vs. 1.41 ± 0.28 g/L, $P < 0.0001$), and APOE levels (43.70 ± 17.13 mg/L vs. 42.60 ± 13.35 mg/L, $P = 0.007$) than the control participants, after with adjustment of age and sex (Table 2). In contrast, significantly lower serum triglyceride (1.47 ± 0.85 mmol/L vs. 1.68 ± 2.10 mmol/L, $P = 0.009$), VLDL (0.75 ± 0.61 mmol/L vs. 1.06 ± 0.60 mmol/L, $P < 0.001$), and Lp(a) levels (123.17 ± 168.89 nmol/L vs. 152.24 ± 200.17 nmol/L, $P = 0.011$) were found in the patients with PACG than in control participants (Table 2). Compared to the patients with PACG, patients with POAG showed significantly higher serum triglyceride (1.57 ± 1.04 mmol/L vs. 1.47 ± 0.85 mmol/L, $P = 0.010$), VLDL (1.28 ± 0.66 mmol/L vs. 0.75 ± 0.61 mmol/L, $P < 0.0001$), APOA (1.46 ± 0.39 g/L vs. 1.40 ± 0.27 g/L, $P < 0.0001$), but mitigated HDL (1.30 ± 0.37 mmol/L vs. 1.35 ± 0.35 mmol/L, $P = 0.009$), with adjustment for age and sex (Table 2). The *P* values of differences in VLDL and APOA surpassed significant levels after the Bonferroni correction.

Multivariate logistic regression analysis confirmed that serum VLDL ($P = 0.002$; odds ratio [OR] = 1.59, 95% CI: 1.18–2.13), APOA ($P < 0.0001$; OR = 3.72, 95% CI: 2.11–6.55), and APOE levels ($P = 0.008$; OR = 1.02, 95% CI: 1.00–1.03) were significantly linked to POAG (Fig. 1A), adjusted for age and sex. Similarly, serum levels of VLDL ($P = 0.001$; OR = 1.70, 95% CI: 1.23–2.36), APOA ($P < 0.0001$; OR = 3.28, 95% CI: 1.78–6.05), APOE ($P = 0.002$; OR = 1.02, 95% CI: 1.00–1.03), and Lp(a) ($P = 0.021$; OR = 1.00, 95% CI: 1.00–1.00) were found to

Table 2 The serum lipid levels in POAG, PACG, and control participants

Parameters	Control ($n=356$)	POAG ($n=1139$)	PACG ($n=1248$)			
	Mean ± SD	Mean ± SD	Mean ± SD	P_1 Value	P_2 Value	P_3 Value
Triglyceride	1.68 ± 2.10	1.57 ± 1.04	1.47 ± 0.85	0.381	**0.009**	**0.010**
Cholesterol (CHO)	4.66 ± 0.95	4.60 ± 0.91	4.72 ± 2.58	**0.043**	0.468	0.219
Low-density lipoproteins (LDL)	2.97 ± 0.85	2.84 ± 0.87	2.92 ± 0.82	0.801	0.496	0.495
High-density lipoproteins (HDL)	1.34 ± 0.35	1.30 ± 0.37	1.35 ± 0.35	0.060	0.865	**0.009**
Very low-density lipoproteins (VLDL)	1.06 ± 0.60	1.28 ± 0.66	0.75 ± 0.61	**< 0.001**	**< 0.001**	**< 0.0001**
Apolipoprotein A (APOA)	1.41 ± 0.28	1.46 ± 0.39	1.40 ± 0.27	**< 0.0001**	0.667	**< 0.0001**
Apolipoprotein B (APOB)	0.98 ± 0.25	0.96 ± 0.29	0.96 ± 0.25	0.662	0.268	0.947
Apolipoprotein E (APOE)	42.60 ± 13.35	43.70 ± 17.13	44.23 ± 16.20	**0.007**	0.103	0.117
Lipoprotein (a) (Lp(a))	152.24 ± 200.17	127.57 ± 190.83	123.17 ± 168.89	0.115	**0.011**	0.396

P_1: POAG vs. Control; P_2: PACG vs. control; P_3: POAG vs. PACG. All P values were adjusted for age and sex. Bold: $P < 0.05$

POAG: Primary open-angle glaucoma. PACG: primary angle-closure glaucoma. SD: standard deviation

Table 3 Serum lipids and lipoproteins' impact on IOP in POAG

Parameters	POAG ($n=1139$)		HTG ($n=865$)		NTG ($n=274$)				
	Mean ± SD	β (95% CI.)	Mean ± SD	β (95% CI.)	Mean ± SD	β (95% CI.)	P_{POAG}	P_{HTG}	P_{NTG}
Triglyceride	1.57 ± 1.04	0.06 (-0.50–0.61)	1.60 ± 1.07	-0.26 (-0.80–0.28)	1.49 ± 0.94	0.15 (-0.56–0.86)	0.845	0.349	0.684
Cholesterol (CHO)	4.60 ± 0.91	-0.75 (-1.38 – -0.12)	4.58 ± 0.91	-0.95 (-1.59 – -0.31)	4.65 ± 0.89	0.04 (-0.56–0.65)	**0.019**	**0.004**	0.894
Low-density lipoproteins (LDL)	2.84 ± 0.87	-0.47 (-1.12–0.18)	2.85 ± 0.90	-0.62 (-1.26–0.03)	2.83 ± 0.77	-0.02 (-0.73–0.69)	0.157	0.062	0.957
High-density lipoproteins (HDL)	1.30 ± 0.37	-2.91 (-4.58 – -1.25)	1.28 ± 0.36	-2.51 (-4.19 – -0.82)	1.38 ± 0.40	1.26 (-0.43–2.95)	**< 0.001**	**0.004**	0.146
Very low-density lipoproteins (VLDL)	1.28 ± 0.66	0.83 (-0.46–2.12)	1.19 ± 0.67	0.54 (-0.75–1.83)	1.14 ± 0.64	-0.02 (-0.98–0.94)	0.210	0.413	0.961
Apolipoprotein A (APOA)	1.46 ± 0.39	-1.92 (-3.86–0.02)	1.43 ± 0.33	-2.75 (-4.69 – -0.81)	1.54 ± 0.54	1.42 (-0.55–3.38)	0.052	**0.006**	0.160
Apolipoprotein B (APOB)	0.96 ± 0.29	-0.70 (-2.62–1.23)	0.96 ± 0.30	-1.06 (-2.97–0.85)	0.94 ± 0.24	-0.14 (-2.32–2.03)	0.480	0.276	0.900
Apolipoprotein E (APOE)	43.70 ± 17.13	0.04 (-0.01–0.09)	44.32 ± 18.61	-0.00 (-0.05–0.05)	41.82 ± 11.40	0.05 (0.00–0.11)	0.149	0.973	0.050
Lipoprotein (a) (Lp(a))	127.57 ± 190.83	-0.00 (-0.01–0.00)	123.82 ± 185.06	-0.00 (-0.01–0.00)	138.89 ± 207.67	0.00 (-0.00–0.00)	0.443	0.531	0.781

All P values were adjusted for age, sex, central corneal thickness, and axial length. Bold: $P < 0.05$

CI: confidence interval. POAG: Primary open-angle glaucoma. HTG: high-tension glaucoma. NTG: normal tension glaucoma. SD: standard deviation

be significantly linked to HTG (Fig. 1B), whereas HDL ($P=0.010$; OR=2.07, 95% CI: 1.19–3.60) and APOA levels ($P<0.0001$; OR=4.91, 95% CI: 2.40–10.05) were significantly associated with NTG (Fig. 1C).

Association of serum lipid and lipoprotein levels with IOPs and IOP fluctuation in POAG patients

Regarding the IOP, multivariate linear regression analysis reported that serum cholesterol ($P=0.019$; β = -0.75, 95% CI: -1.38 – -0.12) and HDL levels ($P<0.001$; β = -2.91, 95% CI: -4.58 – -1.25) were significantly and inversely associated with the IOP level among patients with POAG (Table 3), adjusting for age, sex, CCT, and axial length. Similarly, serum cholesterol ($P=0.004$; β = -0.95, 95% CI: -1.59 – -0.31), HDL ($P=0.004$; β = -2.51, 95% CI: -4.19 – -0.82), and APOA levels ($P=0.006$; β = -2.75, 95% CI: -4.69 – -0.81) showed a significant inverse association with IOP levels among patients with HTG (Table 3). Additionally, serum Lp(a) level was found to be significantly linked to average IOP ($P=0.023$; β = -0.0039, 95% CI: -0.0073 – -0.006) and night peak ($P=0.027$; β = -0.0061, 95% CI: -0.0113 – -0.0008) among patients with POAG (Table 4).

Discussion

Blood lipid and lipoprotein profiles are valuable predictors of chronic diseases and metabolic syndrome [15]. Changes in lipid profiles have been implicated in aging and neurodegenerative disorders [16]. Glaucoma, an age-related neurodegenerative ocular disease, raises concern regarding its association with blood lipid profile [17]. Previous GWAS and cellular studies have identified that the genes ABCA1 and CAV1, responsible for cellular cholesterol transport, are associated with POAG development

Table 4 Association of serum lipid and lipoprotein levels with 24-hour IOPs in patients with POAG

Parameters	IOP peak	IOP trough	IOP fluctuation	Average IOP	Day peak	Night peak
	β coefficient (95% CI), *P value*					
Triglyceride	0.20 (-0.37, 0.77), *0.492*	-0.01 (-0.36, 0.33), *0.940*	0.22 (-0.18, 0.62), *0.274*	0.04 (-0.37, 0.45), *0.839*	-0.202 (-0.71, 0.30), *0.433*	0.37(-0.21, 0.94), *0.211*
Cholesterol (CHO)	-0.30 (-1.04, 0.44), *0.425*	-0.09 (-0.53, 0.34), *0.669*	-0.12 (-0.63, 0.39), *0.652*	-0.19 (-0.71, 0.34), *0.480*	-0.15 (-0.80, 0.51), *0.656*	-0.25 (-0.99, 0.49), *0.510*
Low-density lipoproteins (LDL)	-0.55 (-1.23, 0.14), *0.119*	-0.00 (-0.42, 0.41), *0.982*	-0.43 (-0.91, 0.05), *0.078*	-0.23 (-0.72, 0.26), *0.357*	-0.27 (-0.88, 0.34), *0.385*	-0.55 (-1.24, 0.14), *0.121*
High-density lipoproteins (HDL)	-1.01 (-2.66, 0.63), *0.228*	-0.26 (-1.26, 0.75), *0.617*	-0.74 (-1.89, 0.42), *0.211*	-0.50 (-1.68, 0.68), *0.408*	-0.09 (-1.55, 1.37), *0.907*	-1.27 (-2.93, 0.39), *0.136*
Very low-density lipoproteins (VLDL)	-0.38 (-2.60, 1.84), *0.740*	0.01 (-1.11, 1.13), *0.986*	-0.39 (-2.15, 1.37), *0.668*	-0.38 (-1.68, 0.92), *0.572*	-0.25(-1.72, 1.23), *0.743*	-0.63 (-3.08, 1.82), *0.615*
Apolipoprotein A (APOA)	-0.56 (-1.85, 0.73), *0.396*	-0.46 (-1.24, 0.31), *0.242*	-0.10 (-1.00, 0.79), *0.820*	-0.57 (-1.49, 0.35), *0.224*	-0.25(-1.39, 0.90), *0.675*	-0.75 (-2.05, 0.55), *0.259*
Apolipoprotein B (APOB)	-0.61 (-2.43, 1.20), *0.509*	-0.15 (-1.26, 0.95), *0.786*	-0.33 (-1.59, 0.94), *0.615*	-0.36 (-1.66, 0.94), *0.589*	-0.67 (-2.28, 0.95), *0.420*	-0.39 (-2.23, 1.45), *0.676*
Apolipoprotein E (APOE)	0.04 (-0.06, 0.15), *0.456*	0.04 (-0.02, 0.10), *0.170*	0.02 (-0.07, 0.10), *0.717*	0.03 (-0.04, 0.09), *0.453*	0.05 (-0.03, 0.13), *0.201*	0.01 (-0.10, 0.13), *0.827*
Lipoprotein (a) (Lp(a))	-0.00(-0.00, 0.00), *0.061*	-0.00 (-0.00, 0.00), *0.071*	-0.00 (-0.00, 0.00), *0.235*	-0.00 (-0.00, -0.00), ***0.023***	-0.00 (-0.01, 0.00), *0.060*	0.00 (-0.01, -0.00), ***0.027***

$n = 269$. All P values were adjusted for age, sex, central corneal thickness, and axial length. Bold: $P < 0.05$

CI: confidence interval. POAG: Primary open-angle glaucoma. IOP: intraocular pressure

[6, 7], driving our interest in delineating blood lipid and lipoprotein profiles in patients with POAG.

Results from this study demonstrated that: (1) significantly lower serum cholesterol, but greater VLDL, APOA, and APOE levels were observed in POAG patients in contrast with control participants after adjusting for age and sex; (2) significantly lower serum triglyceride, VLDL, and Lp(a) levels were found in PACG patients contrasting with control participants; (3) significantly higher serum cholesterol, VLDL, and APOA, but lower HDL, were observed in patients with POAG compared to those with PACG; (4) serum levels of VLDL, APOA, APOE, and Lp(a) were significantly associated with HTG, whereas HDL and APOA levels were significantly linked to NTG; (5) serum cholesterol, HDL and APOA levels were inversely connected with IOP among patients with POAG and HTG; (6) serum Lp(a) level was associated with average IOP and night peak in POAG patients.

According to published data, the connection between serum lipids and POAG remains controversial. A previous study revealed a significant connection between serum triglycerides, gamma-glutamyl transferase levels, total bilirubin, and POAG [18]. Similarly, the Korean National Health and Nutrition Examination Survey found a positive connection between raised blood triglyceride levels and POAG in patients undergoing dyslipidemia treatment [19]. Moreover, the Handan Eye Study found that high triglyceride level was an independent risk factor for incident glaucoma in Chinese adults [20]. Nevertheless, the investigation revealed no significant variations in serum triglyceride levels between POAG patients and control participants. Instead, the patients with POAG showed slightly lower total cholesterol levels than control participants, with marginal statistical significance; however, this variation was insignificant in multivariate logistic regression analysis. The controversial association between serum lipids and POAG could be attributed to several factors. First, variations in study designs, such as differences in sample sizes, patient characteristics, and measurement methods of serum lipids and POAG parameters, might lead to inconsistent results. Second, the complexity of the underlying biological mechanisms involving lipid metabolism and glaucomatous optic neuropathy is not fully understood. Additionally, environmental and genetic factors could interact differently in various populations, influencing the observed associations. Nonetheless, the involvement of blood total cholesterol in POAG development requires further investigation.

The function of lipid and lipoprotein profiles in the pathogenesis of PACG remains unclear. In a Saudi cohort, one kind of APOE gene alleles (ε2 allele) at rs429358 and rs7412 was significantly associated with PACG, and ε2-carriers emerged as a predictor for PACG [21]. One cross-sectional study in China found that higher serum APOA, APOB, HDL, and LP(a) levels were linked to a significantly raised PACG risk [14], contradicting these findings. In addition, this study, for the first time, found significantly different serum lipid and lipoprotein profiles in patients with POAG and PACG. It is speculated that this is due to the different pathologic mechanisms underlying POAG and PACG.

In this investigation, for the first time, significantly greater serum VLDL levels were observed in POAG patients as well as in the HTG subgroup than in control participants after adjusting for age and sex. VLDL cholesterol, assembled in the liver and converted to LDL and intermediate-density lipoprotein (IDL) in the bloodstream, contributes to plaque development and atherosclerosis [22]. Recent work revealed a strong connection between glaucoma and atherosclerosis in Chinese patients; 6.5% of patients with primary glaucoma were diagnosed with atherosclerosis compared to the atherosclerosis prevalence of 1.9% in the general population [23]. Additionally, predictive values for cardiovascular events, such as augmentation index and pulse wave velocity, were significantly elevated in POAG patients contrasted with control participants [24]. These phenomena suggest that high serum VLDL levels, which are involved in vascular regulatory dysfunction, may contribute to a higher incidence of atherosclerosis or cardiovascular events in POAG [25].

Lipoproteins serve as cofactors for enzymes and cell-surface ligands, mediating lipid transport in tissues and plasma to maintain cholesterol and triglyceride homeostasis [26]. The major apolipoproteins include APOA (a major component of HDL [27]), APOB (a component of VLDL, IDL, and LDL), and APOE (a component of chylomicrons, VLDL, IDL, LDL, and HDL [28]), all of which are risk factors for atherosclerosis [29], cardiovascular [30], and Alzheimer's disease [31]. Furthermore, Lp(a), which comprises a single LDL-like particle with APOB-100 covalently attached to APOA, is a risk factor for cardiovascular disease [32]. A Polish investigation showed that POAG patients had elevated APOE protein expression levels in both blood and aqueous humor samples compared to the control group [33]. Similarly, research conducted in Japan showed that individuals with POAG had significantly elevated levels of APOE in their aqueous humor compared to those with cataracts [34]. It was consistently demonstrated that individuals with POAG and the HTG subgroup had significantly higher levels of serum APOE compared to control participants. These findings, after accounting for age and sex, imply that APOE may have a role in POAG development. Prior investigations have shown lower APOE levels in aqueous humor specimens from Caucasian POAG patients [35].

Among all the serum lipid indices, APOA was the most consistent and robust, showing statistical significance with POAG and in both the HTG and NTG subgroups, and was highly correlated with IOP. ABCA1 facilitates the movement of cholesterol and phospholipids from within cells to APOA, which produces new HDL particles [36]. APOA has been observed to have reduced in serum and cerebrospinal fluid in several neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, as well as Down syndrome [37]. However, a significantly higher level of APOA-IV was detected in the aqueous humor samples of primary congenital glaucoma patients compared with those of the control participants [38]. This study identified significantly higher serum APOA levels in POAG patients than in control participants but not in patients with PACG after adjusting for age and sex.

Furthermore, total cholesterol was significantly and inversely associated with IOP in patients with POAG and HTG. However, a previous meta-analysis reported that total blood cholesterol was significantly linked to IOP [39]. In the UK Biobank and EPIC-Norfolk cohorts, a greater serum total cholesterol level was linked to elevated corneal-compensated IOP, even after accounting for important demographic, medical, and lifestyle variables [40]. As the effect size was small, this inconsistency could be due to the size and different IOPs used in the studies.

Moreover, in this investigation, HDL and APOA levels were inversely linked to IOP among patients with POAG and HTG. In contrast, higher APOA levels were found in patients with POAG. A recent report showed that a lower HDL level is a POAG risk factor [41]. The potential explanation is as follows: Endothelial nitric oxide synthase (eNOS) is essential for regulating IOP [42] and can be activated by HDL, resulting in increased nitric oxide (NO) production [43, 44]. Therefore, HDL and APOA may contribute to the drainage of the aqueous humor and IOP regulation via the eNOS/NO pathway. Alternatively, HDL cholesterol and APOA may participate in POAG pathogenesis via mechanisms other than IOP regulation. Elevated serum HDL and APOA levels mitigate the progression of neurodegeneration and characteristic clinical manifestations of Alzheimer's disease [45].

Similarly, elevated HDL and APOA levels may serve as a feedback mechanism for neuroprotection against progressive optic nerve degeneration in POAG. Additionally, serum Lp(a) levels were connected with the average IOP and the night peak of 24-hour IOP in POAG patients. However, the other serum lipid and lipoprotein levels were not significantly associated with any indices of 24-hour IOP. Diurnal IOP measurements were typically conducted during office hours. The production of lipids and lipoproteins exhibits circadian rhythmicity [46]. These results suggest that the circadian rhythms of serum lipids and lipoproteins may influence IOP variation over the day/night cycle. Nevertheless, further investigations are needed to fully understand the precise molecular pathways involved.

This investigation contributes the following to the existing knowledge compared to the published studies: First, it had a way larger sample size of 1139 POAG patients and 1248 PACG patients compared to other studies. For instance, the total sample size was only 20

POAG patients in Fu C et al.'s study [47] and 320 PACG patients in Shao M et al.'s study [14]. So, this study had higher statistical power and credibility. Fresh serum samples were detected in this study. Compared with frozen samples in Fu C et al.'s study [47], the results are more accurate and reliable. Second, this study thoroughly compared the serum lipid and apolipoprotein levels among different groups of POAG, PACG, and the normal controls for the first time. The results may reveal the novel different pathologic mechanisms underlying POAG and PACG. Furthermore, this study investigated the association between serum lipid and apolipoprotein levels and 24-hour IOP in POAG.

Strengths and limitations

The highlights of this investigation encompass the following: Firstly, it focused on the Chinese population, providing insights that are relevant to the local community and potentially involving a more targeted understanding of the disease in this demographic context. Secondly, the observational cross-sectional design allowed for a snapshot of the current state of lipid and lipoprotein profiles and their immediate relationship with IOP, offering valuable real-time data. Furthermore, exploring the association with IOP and IOP fluctuation identified potential biomarkers or risk factors that could aid in early diagnosis and intervention for POAG.

This investigation possesses some limitations. First, blood specimens of patients with POAG were obtained only once after enrollment. Multiple measurements during follow-up would be necessary to establish a correlation with POAG progression. Second, the outcomes of the blood lipid and lipoprotein levels might be influenced by underlying disorders or undiagnosed diseases in participants. Third, POAG patients were significantly younger than controls. Differences in sex distribution between study groups were significant. Although the adjustment for age and sex in the multivariate linear regression was carried out, there remained still a possibility of influence from age and sex to the outcomes of blood lipid and lipoprotein levels [16]. Finally, based on the observational cross-sectional investigation, a prospective cohort investigation should be performed to establish causality and additionally investigate the potential benefits of lipid management in glaucoma treatment.

Conclusions

Significantly different serum lipid and lipoprotein profiles were found in patients with POAG and PACG. Furthermore, this study emphasizes the differences in serum lipid and lipoprotein levels among Chinese patients with POAG and their relationship with IOP and IOP fluctuation. Serum lipid and lipoprotein profiles should be considered when evaluating the risk of glaucoma.

Abbreviations

ABCA1	ATP-binding cassette A1
APOA	Apolipoprotein A
APOB	Apolipoprotein B
APOE	Apolipoprotein E
CAV1	Caveolin-1
CCT	Central corneal thickness
CHO	Cholesterol
CI	Confidence interval
GWAS	Genome-wide association study
HDL	High-density lipoprotein
HTG	High-tension glaucoma
IOP	Intraocular pressure
LDL	Low-density lipoprotein
Lp(a)	Lipoprotein A
NTG	Normal tension glaucoma
PACG	Primary angle closure glaucoma
POAG	Primary open-angle glaucoma
SD	Standard deviation
VLDL	Very low-density lipoprotein

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing.

Author contributions

YPY and YHC were responsible for formulating the protocol, composing the protocol and report, executing the search, extracting and scrutinizing data, interpreting findings, and revising the reference lists. XHS, TKN, YHC, and WJC were responsible for formulating the protocol, writing the text, obtaining and scrutinizing the data, and interpreting the findings. YPY, BQ, and TKN participated in the data extraction process and provided valuable input to the text. All authors read and approved the final manuscript.

Funding

Supported by the National Natural Science Foundation of China (82070957, 81870692, 81500715, 82030027, 81790641), SHDC (SHDC2020CR6029), and Shanghai Science and Technology Committee (20S31905800).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study adhered to the Helsinki Declaration and was approved by the Medical Ethics Council of the Eye and ENT Hospital, Fudan University (KJ2011-04). All patients gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 9 May 2024 / Accepted: 23 September 2024
Published online: 30 September 2024

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