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The association between cholesterol levels and severity of normal tension glaucoma

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Purpose: To evaluate the serum lipid levels, including total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) of patients with normal tension glaucoma (NTG) and to investigate the relationship between serum HDL levels and the severity of NTG.

Methods: In this cross-sectional, case-control study, 282 NTG subjects and 202 control subjects were enrolled from the outpatient clinic of the Department of Ophthalmology at Taichung Veterans General Hospital in central Taiwan from 2015 to 2021. Fasting cholesterol, HDL, and LDL levels were evaluated using a biochemical analyzer (ARCHITECT c16000). Glaucoma severity was classified by visual field test as mild (mean deviation [MD] ≥ −6.0dB), moderate (−12dB ≤ MD < −6 dB), and severe (MD < −12dB), based on the mean deviation.

Results: HDL levels were significantly lower in the NTG group compared with the control subjects (47 ± 18mg/dl versus 53 ± 18mg/dl; p = 0.03). There were no statistically significant differences in total cholesterol or LDL levels between the NTG and control subjects (total cholesterol levels: 194 ± 39mg/dl versus 190 ± 32mg/dl; p > 0.05; LDL levels: 113 ± 30mg/dl versus 110 ± 29mg/dl; p > 0.05). The mean serum HDL levels were lowest in the severe group (41 ± 11mg/dl) followed by the moderate (45 ± 16mg/dl) and mild (50 ± 15mg/dl) groups, with significant differences among the three groups (p = 0.02). The multivariate regression analysis revealed a statistically significant negative correlation between HDL and vertical cup-to-disc ratio (VCDR; B =−0.16, p = 0.03) among all NTG patients and a positive correlation between HDL and retinal nerve fiber layer (RNFL; r = 0.34, p = 0.03) among all NTG patients.

Conclusions: A significantly lower serum HDL concentration was found in the NTG patients, which was negatively associated with disease severity. The findings warrant further study to elucidate the role of these phenomena in the pathogenesis of glaucoma.

Normal tension glaucoma (NTG) is a degenerative optic neuropathy characterized by loss of retinal ganglion cells, enlarged cupping of the optic nerve head and visual field defect, and an intraocular pressure (IOP) that does not exceed 21mmHg. NTG is a subtype of primary open-angle glaucoma (POAG) and accounts for approximately 20%–50% of all POAG cases [1]. Because patients with NTG have normal IOP, several hypotheses have been proposed to explain the mechanisms underlying the pathophysiology of NTG, including local or generalized vascular dysregulation, high translaminar cribrosa pressure difference, and low cerebrospinal fluid pressure [2].

There is growing evidence that systemic vascular factors may play a role in NTG pathogenesis [3,4]. Dyslipidemia, which is usually defined as high levels of total cholesterol and triglycerides and/or a low level of high-density lipoproteins (HDL), is one of the most important modifiable risk factors for cardiovascular diseases. Due to its pronounced impact on many organs of the body, dyslipidemia has also been indirectly or directly linked to a wide range of eye diseases, including age-related macular degeneration, glaucoma, retinal vein occlusions, and hypertensive and diabetic retinopathy [5]. Modrzejewska et al. reported that patients with primary open-angle glaucoma had significantly higher total cholesterol and lower HDL levels than normal controls [6]. However, there are conflicting findings in the literature. Some studies have shown that hyperlipidemia had a decreased hazard of open-angle glaucoma [7]. These varying outcomes may be due to differences in types of glaucoma, study design, analysis, and population characteristics among studies. Therefore, we were interested in further exploring the possible relationship between serum cholesterol level and severity of NTG.

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METHODS

Study subjects: Subjects were enrolled from the outpatient clinic of the Department of Ophthalmology at Taichung Veterans General Hospital, Taiwan, from 2015 to 2021. NTG

patients were approached in the clinic while they were seeking treatment. Normal control subjects were also recruited as they visited the outpatient clinic for various reasons. All of the experimental subjects were enrolled after consenting to participate in the study. This study was conducted with the approval of the Human Study Committee of Taichung Veterans General Hospital.

Comprehensive ophthalmologic examinations were performed on all subjects, including visual acuity testing with refraction, IOP measurement, the Humphrey 30-2 visual field test, slit lamp examination, dilated fundoscopy, and optical coherence tomography (OCT) scanning. The definition of NTG included characteristic arcuate, Bjerrum, Seidel and/or paracentral scotoma and/or nasal step on the Humphrey 30-2 with reference to Anderson's criteria for minimal abnormality in glaucoma [8]; corresponding cupping of optic nerve heads and/or nerve fiber layer defects; open anterior chamber angles on gonioscope; and the absence of systemic disorder or a secondary cause for glaucomatous optic neuropathy, such as a previously raised IOP after trauma, a period of steroid administration, or uveitis. Patients also did not have evidence of high myopia or congenital ocular abnormality and had no other cause than glaucoma for disc changes and visual field loss.

Patients with NTG were diagnosed with untreated IOP measurements of 21mmHg or lower on the diurnal test and at follow-up. The Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA) test was used for analysis of clinical parameters, including retinal nerve fiber layer (RNFL) thickness, disc size, cup/disc (C/D) ratio, and rim area. Fasting cholesterol, HDL, and low-density lipoprotein (LDL) levels were evaluated using a biochemical analyzer (ARCHITECT c16000). Glaucoma severity was classified by visual field test as mild (mean deviation [MD] ≥ −6.0dB), moderate (−12dB ≤ MD < −6dB), or severe (MD < −12dB).

Unrelated control subjects were recruited from among patients attending the clinic for conditions such as senile cataract, floaters, refractive errors, or itchy eye. All normal control subjects had no systemic disease and no family history of glaucoma. For the controls, glaucoma was ruled out using the same criteria as used for the NTG patients, who were assessed using the same ophthalmic examination procedure.

Statistical analysis: The independent Student's *t* test and chi-square test were used to compare the characteristics of the NTG patients and the control group. One-way ANOVA with post hoc Scheffe's multiple comparison test was used to compare the levels of lipid and ocular parameters among the three NTG subgroups with different severities. All statistical analyses were performed using SPSS 22.0. We also compared the demographic data among the three groups by using ANOVA for continuous data (age, body mass index [BMI], MD, IOP, central corneal thickness [CCT]) and the chi-square test for binary traits (gender, diabetes, hypertension, use of lipid-lowering medications) and categorical data (family history of glaucoma). To test the correlations between lipid profile and the demographic data, we applied Pearson's correlation for continuous data (age, BMI, MD, IOP, CCT), the *t* test for binary data (gender, diabetes, hypertension), and the ANOVA for categorical data (family history of glaucoma). After conducting the Pearson's correlation, multivariate linear regression analysis was performed to evaluate the associations between HDL and visual field indices (MD), RNFL thickness, and other ocular parameters. A p value of less than 0.05 was considered statistically significant.

RESULTS

Using a cross-sectional, case-control study design, we enrolled 282 NTG subjects and 202 control subjects who attended Taichung Veterans General Hospital, Taiwan, from 2015 to 2021. There were no statistical differences in terms of mean age and gender between the NTG and control groups ($p > 0.05$). Our results showed that HDL levels were significantly lower in the NTG group compared with the control subjects (47 ± 18 mg/dl versus 53 ± 18 mg/dl; $p = 0.03$). There were no statistically significant differences in total cholesterol or LDL levels between the NTG patients and control subjects (total cholesterol levels: 193 ± 39 mg/dl versus 190 ± 32 mg/dl; $p > 0.05$; LDL levels: 113 ± 30 mg/dl versus 110 ± 29 mg/dl; $p > 0.05$; Table 1).

Based on the MD, the NTG subjects were categorized into three subgroups. There were no differences in terms of mean age or gender among these three subgroups. The levels of cholesterol, HDL, and LDL and the ocular characteristics of the three subgroups are presented in Table 2. The ocular parameters, including visual fields (VF) indices, RNFL thickness, and disc rim area were significantly different among the three subgroups ($p < 0.001$). The HDL levels were lowest in the severe subgroup (41 ± 10mg/dl) followed by the moderate (45 ± 17 mg/dl) and mild subgroups (51 ± 15 mg/dl), with significant differences among the three subgroups ($p = 0.02$). There were no significant differences in total cholesterol or LDL levels among the three subgroups ($p > 0.05$).

The associations of visual field MD and RNFL with HDL were small but significantly different from zero ($r = 0.13, 0.21$ and $p = 0.02, 0.01$, respectively). No linear correlations significantly different from zero were observed between HDL and CCT ($r = 0.04$, $p = 0.43$) or between HDL and BMI ($r = -0.04$, $p = 0.33$; Table 3).

Table 1. Comparison of demographics, serum lipid and ocular parameters in NTG and controls.

Variables	NTG	Control	P-value
N	**282**	**202**	
Age (years)	51.8±12.5	54.1±9.8	0.32
Gender (Male/Female)	145/137	102/100	0.9
CCT (µl)	551.1±23.5	550.7±27.9	0.45
IOP (mmHg)	15.8±3.5	16.8±2.4	0.18
VF indices			
MD (dB)	–9.2±3.5	–0.4±0.8	<0.001
PSD (dB)	8.5±1.5	1.3±0.5	<0.001
RNFL thickness (µl)	67.6±13.8	90.1±12.7	<0.001
VCDR	0.62±0.25	0.39±0.19	<0.001
Rim area (mm^2)	1.32±0.36	1.72±0.36	<0.001
Total cholesterol (mg/dl)	193±39	190±32	0.28
LDL (mg/dl)	113±30	110±29	0.44
HDL (mg/dl)	47±18	53±118	0.03

NTG: normal tension glaucoma; CCT: central corneal thickness; IOP: intraocular pressure; VF: visual field; MD: mean deviation; PSD: pattern standard deviation; RNFL: retinal nerve fiber layer; VCDR: vertical cup-disc ratio

There were significant differences in HDL levels between females and males (p = 0.02). No significant differences in HDL levels were observed in cases versus controls in terms of diabetes (48.8 ± 13 in diabetics versus 46.8 ± 12 in controls; p = 0.33) or hypertension (48.3 ± 13 in hypertensives versus 46.8 ± 2 in controls; p = 0.27; Table 4). There were no significant differences in HDL levels between those who did or did not use lipid-lowering medication. Table 5 shows the results of the multiple linear regression analysis of associations between HDL and ocular parameters. In the multivariate regression analysis after adjusting for age, gender, blood pressure, and BMI, there was a statistically significant

Table 2. Comparison of demographics, serum lipid and ocular parameters in NTG subgroups, stratified according to severity.

NTG	Mild	Moderate	Severe	P-value
Number	99	94	89	
Age (years)	52.8±11.6	54.1±12.5	55.8±11.2	0.39
Gender Male/Female	51/48	48/46	46/43	
CCT (µl)	549.1±25.6	554.9±29.0	557.7±27.9	0.47
IOP (mmHg)	15.8±3.7	14.7±2.9	15.3±2.7	0.21
VF indices				
MD (dB)	–3.9±1.4	–9.4±2.3	–20.4±4.8	<0.001
PSD (dB)	3.5±1.4	8.2±2.5	10.8±2.9	<0.001
RNFL thickness (µl)	81.1±13.4	68.4±13.7	55.1±13.7	<0.001
VCDR	0.45±0.16	0.59±0.19	0.80±0.20	<0.001
Rim area (mm^2)	1.71±0.35	1.36±0.35	1.12±0.32	<0.001
Total cholesterol (mg/dl)	191±34	195±37	194±39	0.33
LDL (mg/dl)	113±24	111±26	115±27	0.45
HDL (mg/dl)	51±15	45±17	41±10	0.021

NTG: normal tension glaucoma; CCT: central corneal thickness; IOP: intraocular pressure; VF: visual field; MD: mean deviation; PSD: pattern standard deviation; RNFL: retinal nerve fiber layer; VCDR: vertical cup-disc ratio. Comparison was performed using one-way analysis of variance (ANOVA) with post hoc Scheffe's multiple comparison testing.

Table 3. Pearson's correlations between HDL and age and ocular parameters.

Variables	Correlation coefficient	p value
Age	0.03	0.48
MD	0.13	0.02
CCT	0.04	0.43
VDCR	−0.21	0.03
BMI	−0.04	0.33
RNFL	0.21	0.01
IOP	0.03	0.36

MD: mean deviation; CCT: central corneal thickness; VCDR: vertical cup/disc ratio; BMI: body mass index; RNFL: retinal nerve fiber thickness; IOP: intraocular pressure.

negative correlation between HDL and vertical cup-to-disc ratio (VCDR; B = −0.16, p = 0.03) among all NTG patients. In the mild, moderate, and severe NTG groups, a negative correlation was observed between HDL and VCDR (mild: r = −0.15, p = 0.02; moderate: r = −0.18, p = 0.04; severe: r = −0.15, p = 0.03), and a positive correlation between HDL and RNFL (r = 0.34, p = 0.03) was observed among all of the NTG patients. In the mild and moderate NTG groups, a positive correlation between RNFL and VCDR (mild: r = 0.44, p = 0.02; moderate: r = 0.27, p = 0.04) was observed.

DISCUSSION

The mechanism by which hyperlipidemia increases the risk of glaucoma is unclear. The previous literature has shown that glaucoma may be associated with lipid dysregulation expressed as ocular vascular pathology. Prolonged

Table 4. Correlation between HDL and gender, hypertension and family history.

Trait	p value*	Category	N	Mean HDL (mg/dl)
Gender	**0.02**	**male**	145	45.1±15
		female	137	49.7±14
Diabetes	0.33	**No**	231	48.8±13
		Yes	51	46.8±12
Hypertension	0.27	**No**	160	48.3±13
		Yes	122	46.8±12
Using lipid lowering medication	0.34	**No**	223	46.8±12
		Yes	65	48.5±11
Family history of glaucoma	0.15	**No**	195	49.0±14
		Yes	87	46.9±11

* *t* test p value

Table 5. Multiple linear regressions for association between HDL and ocular parameters.

Normal tension glaucoma B (p value)		
Mild	Moderate	Severe
NS	0.18 (0.03)	0.24 (0.02)
0.44 (0.02)	0.27 (0.04)	NS
−0.15 (0.02)	−0.18 (0.04)	−0.15 (0.03)
NS	NS	NS

MD: mean deviation; RNFL: retinal nerve fiber thickness; VCDR: vertical cup/disc ratio; IOP: intraocular pressure; CCT: central corneal thickness; BMI: body mass index; NS: not significant; analysis adjusted for age, gender, blood pressure and BMI.

disturbances to plasma lipids may lead to degenerative changes in the retinal and choroidal arterioles, venules, and capillaries, which may result in early ischemic angiopathy. A consequence of this process is hypoperfusion, which causes microcirculation disorders related to ganglion cells and may provoke permanent visual disturbances [6]. Oxidative stress-induced apoptosis of the retinal ganglion cells has also been implicated in glaucoma pathogenesis. In glaucomatous patients, extensive DNA damage due to oxidative stress has led to trabecular meshwork injury [9-11]. Furthermore, long-term imbalance in aqueous humor composition can also lead to the apoptosis of trabecular meshwork cells and alteration of the optic nerve head [12]. Ishikawa et al. [13] showed that high serum lipid levels increased peripheral venous pressure and blood viscosity, leading to a decrease in blood outflow [14,15]. Wang et al. [16] found that lipid metabolic abnormalities can change hemodynamics and affect the aqueous humor outflow, which can lead to elevated IOP [17].

This study demonstrated that patients with NTG had lower HDL levels than controls, although there were no significant differences in terms of total cholesterol levels and LDL. HDL has various antioxidant effects throughout the body and is considered protective in cardiovascular disease, thus earning it the moniker “good cholesterol.” HDL possesses several antiatherogenic activities that involve removal of cholesterol and oxysterols from macrophage foam cells, smooth muscle cells, and endothelial cells in the arterial wall. In addition, HDL particles have a protective effect on the vascular endothelium through antioxidative, anti-inflammatory, and antithrombotic activities. Atherosclerosis could consequently reduce blood flow in the eyes, thereby damaging the nerve fibers and leading to retinal ganglion cell (RGC) loss [18].

Lee et al. demonstrated a positive association between hyperlipidemia and OAG with normal IOP in low-teen (IOP ≤ 15 mmHg) OAG patients [19]. Modrzejewska et al. reported that patients with primary open-angle glaucoma had significantly higher total cholesterol and lower HDL levels than normal controls [6]. Kim et al. [5] also demonstrated that low HDL was significantly associated with open-angle glaucoma with normal baseline IOP. However, there are conflicting results in the literature, with some studies reporting no association between hyperlipidemia and glaucoma [20-24] and even a decreased risk of open-angle glaucoma in patients with hyperlipidemia [7]. One systematic review and meta-analysis of observational studies found that patients with glaucoma had higher mean total cholesterol levels and lower HDL levels than patients without glaucoma, but there was no significant difference in terms of LDL [25].

We speculate that the different findings among these studies may be due to the different study populations. In our study, we only included patients with NTG and excluded patients with other types of glaucoma. In contrast, Posch-Pertl et al. included studies that enrolled patients with NTG, pseudoexfoliation glaucoma, open-angle glaucoma, and glaucoma [25]. Madjedi et al. suggested that serum total cholesterol, HDL, and LDL were positively associated with IOP in two UK cohorts and that triglyceride levels may have been negatively associated [26]. This study attributed the relationships between IOP regulation and lipid metabolism in part to genetics. Genetic associations have been identified between single nucleotide polymorphisms associated with IOP and single nucleotide polymorphisms associated with lipid metabolism [26].

To the best of our knowledge, this is the first study to investigate the relationship between lipid profile and NTG severity. Our data suggest the presence of significantly lower HDL levels in NTG patients and a negative association of HDL with disease severity. Based on the MD, the NTG subjects were categorized into three subgroups based on level of severity (mild, moderate, or severe). The mean serum levels of HDL were lowest in the severe NTG subgroup followed by the moderate NTG and mild NTG subgroups. There were also statistically significant negative correlations between HDL and VCDR as well as HDL and MD, in addition to a positive correlation between HDL and RNFL. Because these correlations may also be affected by other factors, multivariate analysis was conducted to further investigate the association between HDL and glaucoma. The results showed that there was also a significant correlation between HDL and VCDR, between HDL and MD, and between HDL and RNFL. In conclusion, we hypothesize that the mean serum level of HDL was associated with NTG severity.

This is the first study to specifically explore the relationship between lipid profile and NTG severity; however, this investigation has some limitations. First, this study was a retrospective case-control study; hence, causality cannot be presumed. Second, our subjects may not have been representative of the general population. Hospital-based studies may have detection biases because individuals with comorbidities, such as diabetes or hypertension, are likely to receive more frequent eye examinations than the general population and are therefore more likely to be diagnosed with glaucoma. Third, there were significant differences in HDL levels between females and males ($p = 0.02$). However, the ratio between males and females was similar between the NTG group and control subjects as well as among the three different NTG severity subgroups. Despite these limitations,

our results provide a valuable contribution to our growing understanding of the influence of HDL on disease pathology and may help to shed light on the pathophysiology of glaucoma. Furthermore, as HDL is a protective and modifiable factor, the findings of this study could be helpful in managing the severity of glaucoma by targeting HDL.

In conclusion, patients with severe glaucoma had lower serum HDL levels compared with normal subjects and those with early or moderate glaucoma. Further multicenter, prospective studies consisting of large patient samples are warranted to confirm these findings.

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