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Association of Hypertriglyceridemia and Incident Glaucoma in a Rural Chinese Population: The Handan Eye Study

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Received: January 17, 2021
Accepted: June 14, 2021
Published: July 28, 2021

Keywords: metabolic risk factors; incident glaucoma; population-based; cohort study

Citation: Zhang Y, Zhang Q, Thomas R, Li SZ, Wang NL. Association of hypertriglyceridemia and incident glaucoma in a rural Chinese population: The Handan Eye Study. Transl Vis Sci Technol. 2021;10(8):25, https://doi.org/10.1167/tvst.10.8.25

Purpose: The purpose of this paper was to investigate the association between baseline metabolic risk factors and incident glaucoma over a 5-year period in rural Chinese adults.

Methods: Population-based prospective cohort study. Participants aged 30 years and older without glaucoma at baseline who underwent comprehensive examinations at baseline and after a 5-year interval in the Handan Eye Study were enrolled. Incident glaucoma was defined as people without glaucoma in either eye at baseline that had developed glaucoma in at least one eye in the 5-year follow-up. Five metabolic syndrome components, mean blood pressure, fasting plasma glucose, total cholesterol, triglycerides (TGs), low density lipoprotein cholesterol, high-density lipoprotein cholesterol, and obesity, determined as body mass index $\geq$30 kg/m^2 at baseline were considered as potential metabolic risk factors for incident glaucoma. Univariate and multivariate logistic regression analyses were carried out to determine baseline metabolic risk factors associated with incident glaucoma.

Results: A total of 5184 participants were included in our study. During the 5-year follow-up, incident glaucoma developed in 82 subjects. Age (odds ratio [OR] = 1.060, 95% confidence interval [CI] = 1.034, 1.086, $P < 0.001$) and TGs level (OR = 1.213, 95% CI = 1.030, 1.429, $P = 0.021$) were independently and positively associated with incident glaucoma.

Conclusions: Our study revealed that increased age and high TGs level, one of the baseline metabolic features, were independent risk factors for incident glaucoma. The data implied that the metabolic features be involved in the pathogenesis of glaucoma.

Translational Relevance: This study shed the light on that the TGs level was involved in the pathogenesis of glaucoma.

Introduction

Glaucoma, the leading cause of irreversible blindness worldwide, is a progressive optic nerve disease often associated with elevated intraocular pressure (IOP), and characterized by optic disc cupping and visual field defects.[1,2] It has been predicted that there are over 75 million patients with glaucoma in 2020, and will increase to over 110 million in 2040.[3]

High IOP is considered to be the most common and modifiable risk factor for the development of glaucoma. However, because not all patients with elevated IOP develop glaucoma and many patients develop glaucoma despite a normal IOP, elevated IOP does not seem sufficient to solely explain the pathogenesis of glaucoma.[4] Hence, other risk factors may contribute to optic nerve damage or disease progression in glaucoma, including structural abnormalities and insufficient blood flow supplying the optic nerve

and the surrounding retinal tissue caused by the dysfunction of the vasculature.[5,6]

Although the underlying mechanisms currently remain unclear, many previous cross-sectional and longitudinal epidemiological studies have shown associations of glaucoma or elevated IOP with several metabolic complications, such as elevated blood pressure (BP), elevated fasting plasma glucose (FPG) levels, concurrent atherosclerotic disease, and possibly obesity.[7–15] These findings suggest a common underlying mechanism linking elevated IOP or glaucoma to various related metabolic risk factors, in other words, some or all components of metabolic syndrome (MetS).

MetS is a cluster of disorders and also atherosclerotic risk factors, including abdominal obesity, dyslipidemia (elevated triglycerides [TGs] and/or low high-density lipoprotein cholesterol [HDL-C]), raised BP, and hyperglycemia.[16,17] The MetS was defined as having at least three of the five components.[16,17]

We hypothesized that metabolic risk factors might be involved in the pathogenesis of glaucoma. A prospective cohort study is the standard method for exploring and identifying risk factors associated with a certain incident disease. In this study, we analyzed the relationships between the metabolic components including dyslipidemia, elevated BP, elevated waist circumference (WC), hyperglycemia, and obesity, and the incident glaucoma in a Northern rural Chinese population, through the 5-year follow-up and baseline researches of the Handan Eye Study (HES).

Methods

Subjects and Examination

The HES baseline examination was conducted from 2006 to 2007. Residents aged 30 years or more who resided in the 13 targeted villages of Yongnian County, Handan City, Hebei Province, northern China for at least 6 months were recruited.[18] The detailed methods and procedures of the HES has been published.[18] A total of 6830 participants took part in the baseline prevalence study.[18] The health check-up included the standardized eye examination, physical examination, interview, and laboratory examination at a central clinic in the county hospital or locally established test centers.[18] Home visits were conducted when subjects were unable to attend the local examination center.[18]

A standardized 5-year follow-up examination and an interview were conducted from 2012 to 2013 adhering to the same protocol as baseline. All available participants from the baseline study were invited to take part.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Beijing Tongren Hospital (approval number: TREC2006-22). Written informed consent was obtained from all participants.

Data Collection

According to standardized protocols at both baseline and follow-up visits, all participants underwent a comprehensive ophthalmic examination, including autorefraction using a KR-8800 auto keratorefractometer (Topcon, Tokyo, Japan), visual acuity using the logMAR E chart, subjective refraction, slit-lamp examination, anterior segment optical coherence tomography (OCT) imaging using the Visante anterior segment OCT (Carl Zeiss, Jena, Germany), IOP measurement using Kowa applanation tonometer (Kowa Company Ltd., Tokyo, Japan), ocular biometry using a 10-MHz A/B-mode ultrasound device (CineScan; Quantel Medical, Clermont-Ferrand, France), by a hard-tipped, corneal contact probe mounted on a slit lamp at baseline and an OcuScan RxP (Alcon, Inc., Fort Worth, TX, USA) at the follow-up, lens grading using the Lens Opacification Classification System III (LOCS III), fundus photography, and retinal nerve fiber layer (RNFL) imaging.[18,19]

Fundus photography was performed using Topcon TRC-NW6S/7S camera (Topcon, Tokyo, Japan) at baseline. And at follow-up, a Topcon TRC-NW6S/7S camera (Topcon, Tokyo, Japan) was used for approximately one-third of study participants, and a Canon CR-DGi with a 20D SLR back (Canon, Tokyo, Japan) was used for the other two-thirds of subjects. RNFL imaging was performed using Stratus OCT (Carl Zeiss, Jena, Germany) at baseline and RTVue (Carl Zeiss Meditec, Dublin, CA, USA) at follow-up.

Visual field testing using the standard 24-2 Swedish Interactive Testing Algorithm standard program on a visual field analyzer (Humphrey Visual Field Analyzer 740i or 750i; Carl Zeiss, Jena, Germany) and gonioscopy was performed on 1 in 10 subjects as well as who were found to have limbal anterior chamber depth (LACD) $\leq$40%, IOP $>$21 mm Hg, and those having a history of glaucoma or suspect. The visual field was retested 20 minutes later if the glaucoma hemifield test result was outside the normal limits or was borderline or if the test was unreliable (i.e. fixation loses $\geq$20%, false positives $\geq$33%, or false negatives $\geq$33%).

Baseline and follow-up systemic characteristics of participants were collected. During the physical

examination, anthropometric measurements including height, weight, WC, hip circumference (HC), and BP were conducted according to standardized protocols by certified nurses.

Body height and weight were measured with subjects standing in bare feet and without outerwear. Height measurements were taken with a wall-mounted measuring tape. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. WC was measured at the mid-point on the midaxillary line between the lowest border of the last rib and the top of the iliac crest. HC was measured at the widest part of the hip at the lever of the greater trochanter. Waist to hip ratio (WHR) was calculated as WC divided by HC.

Two separate BP measurements were obtained with the subject in the seated position after 5 minutes of rest by using the noninvasive, automated electronic device (Hem-907 at baseline and Hem-7201 at follow-up, OMRON, Japan). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as the mean of the two independent measures. A third measurement was performed if the difference was >10 mmHg between the 2 SBP readings or >5 mm Hg between the 2 DBP readings, in which case, the mean of the 2 closer readings was used. Mean blood pressure (MBP) was calculated as (SBP + 2 × DBP) / 3.

Trained interviewers employed from local hospital or medical schools used questionnaires to obtain information regarding sociodemographic characteristics, occupation, education, health behavior (smoking, alcohol use, and physical activity), personal medical conditions, and familial medical histories from subjects. Smoking and alcohol use were defined as never used, current user, and former user.

Every subject who agreed to participate in the baseline study was requested to fast for at least 8 hours prior to blood drawing. Fasting venous blood samples were obtained early in the morning (7:00 to 9:00 AM) and blood centrifugation was done on site soon after blood collection with samples stored in an icebox prior to transfer to the hospital refrigerator. Serum was analyzed for lipids, including total cholesterol (TC), TGs, HDL-C, and low-density lipoprotein cholesterol (LDL-C), FPG, and et al.

Glaucoma Diagnostic Definitions at Follow-up

The diagnosis of glaucoma in the follow-up research of the HES study had three steps. First, stereoscopic optic disc photographs at follow-up were evaluated by four glaucoma specialists (YZ, QZ, JH, and ZG). The status of the optic nerve was categorized as "definite glaucoma," "probable glaucoma," "possible glaucoma," and "not glaucoma." Vertical cup-disc ratio (VCDR), notching of the neural rim, localized or diffuse loss of the neural rim, presence of neural rim tissue ≤0.1, and presence of a nerve fiber layer defect were all documented. Those felt to have definite glaucoma, probable glaucoma, and possible glaucoma by any of the specialists were presented to a panel of glaucoma specialists in the next step.

Second, three senior glaucoma specialists (TR, BSW, and YBL), reviewed the follow-up disc photographs of subjects who were classified as definite glaucoma, probable glaucoma, or possible glaucoma in the first step again and categorized these subjects as having definite, probable, possible, or no glaucoma based on consensus. If the results differed among three specialists, a third independent reading was carried out by another senior glaucoma specialist (DSF), who also classified the patients according to the same definitions based on the follow-up fundus photographs.

The final diagnosis was determined by another glaucoma specialist (NLW) based on disc photographs, clinical records for VCDRs and visual fields in the follow-up research if some confused diagnosis existed in the second step. In addition, the disc morphology changes comparing to the baseline were used only when it was still confusing for some cases in the final step diagnosis. Those graded with definite or probable glaucoma using the review described were ultimately classified as having glaucoma. The changes in visual field compared to the baseline of subjects were not evaluated in the glaucoma diagnosis procedure.

Glaucoma was also diagnosed as present in persons in whom the optic nerve was not visible because of media opacity, visual acuity was 20/400, and IOP was 99.5th percentile; or in whom visual acuity was 20/400, and the eye had evidence of previous glaucoma filtering surgery; or if medical records were available confirming glaucomatous damage.

Incident glaucoma was defined as people without glaucoma in either eye at baseline who developed glaucoma in at least one eye in the 5-year follow-up.

Definition of Risk Factors

The baseline demographic information, including age and sex, anthropometric data including BMI, WHR, the health behavior including smoke and alcohol intake, and medical history including stroke, heart disease, and hyperlipidemia, were all considered as potential risk factors for incident glaucoma.

The clinical diagnosis of MetS was made according to the revised National Cholesterol Education Program Adult Treatment Panel III criteria (2004) with waist circumference cutoff modified for an Asian population.[20,21] There are 5 components in the MetS diagnosis: (1) elevated WC: WC ≥90 cm in male subjects and ≥80 cm in female subjects; (2) elevated TGs: ≥1.7 mmol/L; (3) reduced HDL-C: <1.0 mmol/L in male subjects and <1.3 mmol/L in female subjects; (4) elevated BP: SBP ≥130 mm Hg and/or DBP ≥85 mm Hg or under antihypertensive drug treatment in a patient with a history of hypertension; and (5) hyperglycemia: FPG ≥5.6 mmol/L or use of antidiabetic medications.[20,21]

The five MetS components at baseline were all defined as potential metabolic risk factors for incident glaucoma in our study. Besides those, MBP, laboratory data, including FPG, TC, TGs, LDL-C and HDL-C, and obesity, determined as BMI ≥30 kg/m^2 at baseline were also considered as potential metabolic risk factors for incident glaucoma.[22]

Statistical Analysis

All statistical analysis was performed with Statistical Package for the Social Sciences version 25.0 (Chicago, IL, USA). Baseline characteristics were compared between subjects who did not return for follow-up examination or had ungradable fundus photographs and those who did receive the follow-up examination. Comparison of baseline characteristics and possible risk factors between subjects who did not develop glaucoma in the follow-up and those who did was also performed. Subjects who were on treatment for hyperlipidemia were excluded for calculation of lipid levels (including TC, TGs, LDL-C, and HDL-C).

For the continuous variables, the data were tested for normality using the Kolmogorov-Smirnov test. Comparison of variables was done using the independent *t*-test (for variables demonstrating a normal distribution) or Mann-Whitney U test (for variables failing to demonstrate a normal distribution) for continuous variables, and Pearson's χ^2 test for categorical variables.

Univariate and multivariate logistic regression analyses were carried out to determine risk factors at baseline associated with incident glaucoma and to calculate the odds ratios (ORs) and their 95% confidence intervals (CIs) for incident glaucoma. The following possible risk factors previously mentioned were tested: age, sex, history of stroke, history of heart disease, history of hyperlipidemia, smoking, drinking, IOP, BMI, WHR, MBP, FPG, TC, TGs, LDL-C and HDL-C, elevated BP, hyperglycemia, elevated WC, elevated TGs, reduced HDL-C, and obesity. Variables found to be significant (with $P < 0.1$) in univariable analysis were then added to the multivariable analysis. Statistical significance was set at $P < 0.05$.

Results

A total of 5394 subjects aged 35 years or older participated in the 5-year follow-up of the HES. There were 1436 subjects who were lost to follow-up due to the following reasons: (1) died (507 subjects, 35.3%), (2) had severe physical or mental diseases (117 subjects, 8.1%), (3) were at work (496 subjects, 34.5%), (4) refused to attend (251 subjects, 17.5%), (5) were out of contact (63 subjects, 4.4%), and (6) documented with the wrong information (2 subjects, 0.1%), leaving 5394 participants completed in the follow-up study.[19] The follow-up rate of the HES was 85.3%.[19] Among the 5394 subjects with follow-up reexamination, 83 were diagnosed with glaucoma and 3 with undetermined diagnosis at baseline; 124 could not be diagnosed at follow-up because of no readable fundus photographs. Finally, the remaining at-risk population comprised 5184 participants (82.0%) in our study (Figure).

There were 702 subjects who had no blood samples collected, leaving 4482 of the 5184 subjects who had complete data on all laboratory variables. The amount of missing data was 13.5% for each variable obtained from the blood samples.

The baseline characteristics of the participants and nonparticipants in this study are summarized in Table 1. Compared with the 1139 nonparticipant survivors, the 5184 participant survivors tended to have better BCVA ($P < 0.001$), smaller LT ($P < 0.001$), smaller VCDR ($P = 0.012$), larger BMI ($P = 0.001$), and higher MBP ($P = 0.008$).

At the 5-year follow-up, 82 subjects were diagnosed with incident glaucoma (definite and probable glaucoma). A total of 81 subjects were on treatment for hyperlipidemia including 2 incident glaucoma and 79 nonincident glaucoma subjects. The data of these subjects were excluded for calculation of lipid levels. Baseline characteristics and components of MetS of participants with and without incident glaucoma are shown in Table 2. Analysis of these baseline parameters showed that compared with those who did not develop glaucoma over the 5-year period, the incident cases were more likely to be older ($P < 0.001$), smoked currently or in the past ($P = 0.023$), had worse BCVA ($P = 0.001$), had higher IOP ($P = 0.016$), had shallower central anterior chamber depth (ACD; $P = 0.007$), had thicker lenses ($P = 0.002$), had larger

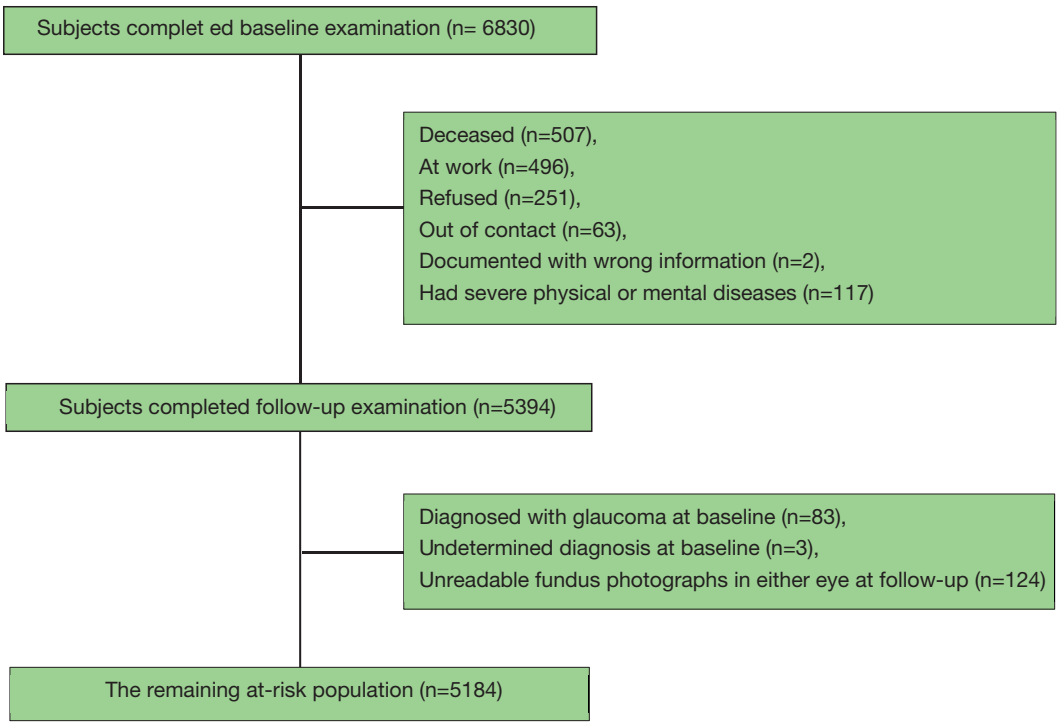

Figure. Flow chart showing the enrollment of participants in this study.

VCDR ($P < 0.001$), had higher MBP ($P = 0.002$) and elevated BP ($P < 0.001$), had higher TC level ($P = 0.027$) and LDL-C level ($P = 0.021$) at baseline.

In univariate regression analysis, age (OR = 1.073, 95% CI = 1.051, 1.095, $P < 0.001$), smoking (in the past; OR = 2.715, 95% CI = 1.271, 5.799, $P = 0.010$), IOP (OR = 1.105, 95% CI = 1.029, 1.187, $P = 0.006$), MBP (OR = 1.025, 95% CI = 1.010, 1.040, $P = 0.001$), TC level (OR = 1.282, 95% CI = 1.018, 1.616, $P = 0.035$), TGs level (OR = 1.217, 95% CI = 1.051, 1.409, $P = 0.009$), LDL-C level (OR = 1.452, 95% CI = 1.032, 2.042, $P = 0.032$), and elevated BP (OR = 3.184, 95% CI = 1.754, 5.778, $P < 0.001$) were positively associated with incident glaucoma (Table 3). After including these five parameters in the multivariate regression analysis (backward), the result showed that age (OR = 1.060, 95% CI = 1.034, 1.086, $P < 0.001$) and TGs level (OR = 1.213, 95% CI = 1.030, 1.429, $P = 0.021$) were independently associated with incident glaucoma (see Table 3).

Discussion

To the best of our knowledge, this is the first large, population-based cohort study to examine the associations between metabolic risk factors and incident glaucoma in an adult Chinese population. In this longitudinal study comprising Chinese adults age 30 years or older who participated in both the baseline and 5-year follow-up of the HES, we found that age and TGs level, one of the metabolic features, were positively and independently associated with incident glaucoma. In our study, subjects with incident glaucoma had higher TGs level than those without, but the difference failed to show statistical significance. This is likely due to the limited number of patients with incident glaucoma on follow-up.

Hypertriglyceridemia is an independent risk factor for cardiovascular disease, often seen in patients with metabolic syndrome and type 2 diabetes.[23,24] A significant association among high TGs level, a metabolic factor, and glaucoma has been reported before.[7,25–27] A meta-analysis included 17 case-control studies investigating the difference in TGs levels in patients with glaucoma and those without found that patients with glaucoma had significantly higher mean TGs level than patients without glaucoma.[25] Another meta-analysis, which included 28 studies, also reported that hypertriglyceridemia showed a significant association with glaucoma.[28] As the studies included in this meta-analysis were case-control studies, whether the association is causal or not remains to be investigated.[25] In addition, the exact role of TGs in the pathogenesis and progression of glaucoma remains unclear.[25]

Patients diagnosed with glaucoma have been shown to have an increased risk of cardiovascular mortal-

Table 1. Comparison of Baseline Characteristics of Participants and Nonparticipants in This Study

Parameter	Nonparticipants ($n = 1139$)	Participants ($n = 5184$)	*P* Value
Age (IR), years	51.0 (39.0, 61.0)	52.0 (42.0, 58.0)	0.761†
Gender			
Male (%)	537 (47.1)	2327 (44.9)	0.166‡
Female (%)	602 (52.9)	2857 (55.1)	
BCVA (IR)	0.10 (0.00, 0.20)	0.10 (0.00, 0.10)	<0.001†
IOP (IR), mm Hg	15.3 (13.0, 17.3)	15.0 (13.0, 17.0)	0.090†
Central ACD (IR), mm	2.76 (2.42, 3.06)	2.73 (2.44, 3.01)	0.090†
LT (IR), mm	4.63 (4.30, 4.96)	4.69 (4.39, 4.98)	<0.001†
AL (IR), mm	22.81 (22.32, 23.34)	22.79 (22.27, 23.28)	0.106†
VCDR (IR)	0.40 (0.40, 0.50)	0.40 (0.40, 0.40)	0.012†
BMI (IR), kg/m^2	23.67 (21.64, 26.42)	24.22 (22.10, 26.44)	0.001†
WHR (IR)	0.90 (0.86, 0.94)	0.90 (0.87, 0.93)	0.142†
MBP (IR), mm Hg	95.3 (86.0, 104.7)	96.3 (87.5, 106.3)	0.008†
FPG, mmol/L	5.53 (5.20, 5.94)	5.51 (5.18, 5.93)	0.387†
TC (IR), mmol/L	4.51 (3.92, 5.20)	4.51 (3.95, 5.15)	0.883†
TGs (IR), mmol/L	1.23 (0.90, 1.81)	1.25 (0.88, 1.81)	0.987†
LDL-C (IR), mmol/L	2.65 (2.25, 3.13)	2.65 (2.26, 3.08)	0.909†
HDL-C (IR), mmol/L	1.24 (1.09, 1.42)	1.25 (1.09, 1.43)	0.749†

BCVA, best corrected visual acuity; IOP, intraocular pressure; ACD, anterior chamber depth; LT, lens thickness; AL, axial length; VCDR, vertical cup disc ratio; BMI, body mass index; WHR, waist hip ratio; MBP, mean blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TGs, total triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; WC, waist circumference; IR, interquartile range.

†Mann-Whitney U test.

‡χ^2 test.

ity, which is primarily explained by common risk factors, such as hypertriglyceridemia.[29–32] The mechanism may be that hypertriglyceridemia causes vascular dysfunction that leads to abnormal ocular blood flow and perfusion instability leading to impaired vascular supply to the optic nerve head and / or increased blood viscosity, which causes elevation of episcleral venous pressure resulting in increased IOP.[25,33–35]

Our study explored the relationship between baseline IOP and TGs level and found that TGs level were positively associated with IOP (OR = 0.267, 95% CI = 0.346, 0.425, $P < 0.001$; not shown in the results section). Previous studies had also reported a similar association. Chang et al. analyzed the clinical data of 1112 participants in Taiwan and concluded that DBP, FPG, and TGs level were positively associated with IOP.[7] Yi et al. investigated the relationship between ocular hypertension and MetS in 17,160 Korean adults and found out that elevated FPG, elevated BP, elevated TGs, and low HDL-C were associated with higher IOPs.[36] Yokomichi et al. included 15,747 Japanese individuals who visited a private healthcare center and found that increases in HDL-C, TGs, SBP, DBP, and FPG levels were risk factors for elevated IOP.[37] Wang et al. included 3251 Chinese individuals (age ≥45 years) from the Beijing Eye Study and found that patients with dyslipidemia had significantly increased IOP but failed to find any significant relationship between dyslipidemia and glaucoma.[38]

At this stage, we cannot determine whether hypertriglyceridemia leads to incident glaucoma via a potential effect on IOP, or whether TGs may have a pathogenic impact on glaucoma independently of IOP.

Besides the TGs level, other metabolic risk factors were also found to be associated with glaucoma or increased IOP. Zhao et al. reported a meta-analysis which identified 47 studies, including 2,981,342 individuals from 16 countries and found that diabetes, diabetes duration, and FPG levels were associated with a significantly increased risk of glaucoma; diabetes and FPG levels were associated with slightly higher IOP.[39] Jung et al. published a study, which included 287,553 subjects using the Korean National Health Insurance System and found that high FPG, BP, and TC levels were all associated with increased risk of developing primary open angle glaucoma (POAG).[40] Rasoulinejad et al. included 200 Iranian subjects (100 patients with

Table 2. Comparison of Subjects With and Without Incident Glaucoma in This Study

Parameter	Subjects Who Developed Glaucoma ($n = 82$)	Subjects Who Did Not Develop Glaucoma ($n = 5102$)	*P* Value
Age (IR), years	60.0 (52.0, 67.3)	52.0 (42.0, 58.0)	<0.001†
Gender			
Male (%)	42 (51.2)	2285 (44.8)	0.245‡
Female (%)	40 (48.8)	2817 (55.2)	
History of stroke			
No (%)	74 (94.9)	4875 (97.8)	0.096‡
Yes (%)	4 (5.1)	109 (2.2)	
History of heart disease			
No (%)	70 (92.1)	4569 (94.9)	0.289‡
Yes (%)	6 (7.9)	248 (5.1)	
History of hyperlipidemia			
No (%)	66 (95.7)	4388 (97.6)	0.227‡
Yes (%)	3 (4.3)	106 (2.4)	
Smoking			
Current (%)	20 (25.3)	1376 (27.3)	0.023‡
Past (%)	8 (10.1)	200 (4.0)	
Never (%)	51 (64.6)	3462 (68.7)	
Drinking			
Current (%)	12 (15.2)	948 (18.8)	0.704‡
Past (%)	2 (2.5)	137 (2.7)	
Never (%)	65 (82.3)	3952 (78.5)	
BCVA (IR)	0.10 (0.00, 0.20)	0.00 (0.00, 0.10)	0.001†
IOP (IR), mm Hg	16.00 (13.50, 17.75)	15.0 (13.0, 17.0)	0.016†
Central ACD (IR), mm	2.57 (2.26, 2.91)	2.73 (2.45, 3.01)	0.007†
LT (IR), mm	4.82 (4.50, 5.29)	4.68 (4.39, 4.98)	0.002†
AL (IR), mm	22.77 (22.33, 23.44)	22.79 (22.27, 23.28)	0.713†
VCDR (IR)	0.50 (0.40, 0.60)	0.40 (0.40, 0.40)	<0.001†
BMI (IR), kg/m^2	24.44 (21.67, 26.67)	24.22 (22.10, 26.44)	0.886†
WHR (IR)	0.91 (0.88, 0.94)	0.90 (0.87, 0.93)	0.193†
MBP (IR), mm Hg	102.3 (90.8, 112.8)	96.17 (87.33, 106.17)	0.002†
FPG, mmol/L	5.54 (5.32, 5.88)	5.51 (5.17, 5.93)	0.365†
TC (IR), mmol/L	4.89 (4.16, 5.38)	4.50 (3.95, 5.13)	0.027†
TGs (IR), mmol/L	1.29 (0.84, 2.05)	1.24 (0.88, 1.79)	0.531†
LDL-C (IR), mmol/L	2.95 (2.36, 3.25)	2.64 (2.26, 3.06)	0.021†
HDL-C (IR), mmol/L	1.25 (1.06, 1.44)	1.25 (1.09, 1.43)	0.855†
Elevated BP (BP ≥130/85 mm Hg or use of antihypertensive medications)			
No (%)	13 (16.0)	1924 (37.8)	<0.001‡
Yes (%)	68 (84.0)	3161 (62.2)	
Hyperglycemia (FBG ≥5.6 mmol/L or use of antidiabetic medications)			
No (%)	39 (56.5)	2450 (55.7)	0.886‡
Yes (%)	30 (43.5)	1952 (44.3)	
Elevated WC (≥90 cm in men or 80 cm in women)			
No (%)	30 (38.0)	2064 (40.7)	0.620‡
Yes (%)	49 (62.0)	3003 (59.3)	
Elevated TGs (≥1.70 mmol/L)			
No (%)	43 (64.2)	3099 (71.5)	0.187‡
Yes (%)	24 (35.8)	1234 (28.5)	
Reduced HDL-C (<1.0 mmol/L in men or 1.3 mmol/L in women)			
No (%)	41 (61.2)	2744 (63.3)	0.718‡
Yes (%)	26 (38.8)	1590 (36.7)	
Obesity (BMI ≥30 kg/m^2)			
No (%)	74 (93.7)	4616 (93.1)	0.848‡
Yes (%)	5 (6.3)	341 (6.9)	

BCVA, best corrected visual acuity; IOP, intraocular pressure; ACD, anterior chamber depth; LT, lens thickness; AL, axial length; VCDR, vertical cup disc ratio; BMI, body mass index; WHR, waist hip ratio; MBP, mean blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TGs, total triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; WC, waist circumference; IR, interquartile range.

†Mann-Whitney U test.

‡χ^2 test.

POAG and 100 controls) and found that patients with elevated FPG, high BP, and high TGs level had significantly higher IOP levels and patients with glaucoma had increased prevalence of components of MetS.[41] Kim et al. included 18,240 Korean participants who underwent health check-ups and found that normal

Table 3. Baseline Metabolic Risk Factors for Incident Glaucoma in This Study

	Univariate Logistic Regression		Multivariate Logistic Regression			
Variable	OR (95% CI)	*P* Value	Estimated Regression Coefficient	χ^2	OR (95% CI)	*P* Value
Age	1.073 (1.051, 1.095)	<0.001	0.058	21.598	1.060 (1.034, 1.086)	<0.001
Female sex	0.773 (0.499, 1.195)	0.247				
History of stroke, present	2.418 (0.868, 6.730)	0.091	—-	—-	—-	—-
History of heart disease, present	1.579 (0.679, 3.671)	0.288				
History of hyperlipidemia, present	1.882 (0.582, 6.081)	0.291				
Smoking						
Never	reference	reference				
Current	0.987 (0.586, 1.661)	0.960				
Past	2.715 (1.271, 5.799)	0.010	—-	—-	—-	—-
Drinking						
Never	reference	reference				
Current	0.770 (0.414, 1.430)	0.408				
Past	0.888 (0.215, 3.662)	0.869				
IOP	1.105 (1.029, 1.187)	0.006	—-	—-	—-	—-
BMI	0.990 (0.930, 1.055)	0.762				
WHR	26.768 (0.420, 1704.897)	0.121				
MBP	1.025 (1.010, 1.040)	0.001	—-	—-	—-	—-
FPG	1.100 (0.973, 1.243)	0.129				
TC	1.282 (1.018, 1.616)	0.035	—-	—-	—-	—-
TGs	1.217 (1.051, 1.409)	0.009	0.193	5.329	1.213 (1.030, 1.429)	0.021
LDL-C	1.452 (1.032, 2.042)	0.032	—-	—-	—-	—-
HDL-C	0.670 (0.273, 1.648)	0.383				
Elevated BP, present	3.184 (1.754, 5.778)	<0.001	0.663	3.422	1.941 (0.961, 3.919)	0.064
Hyperglycemia, present	0.965 (0.598, 1.560)	0.886				
Elevated WC, present	1.123 (0.710, 1.774)	0.620				
Elevated TG, present	1.489 (0.911, 2.434)	0.112				
Reduced HDL-C, present	1.177 (0.725, 1.911)	0.509				
Obesity, present	0.915 (0.367, 2.278)	0.848				

IOP, intraocular pressure; BMI, body mass index; WHR, waist hip ratio; MBP, mean blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TGs, total triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; WC, waist circumference; OR, odds ratio; CI, confidence interval.

tension glaucoma was positively associated with the number of MetS components.[42]

In our study, using logistic regression analysis, only high TGs level, but not other metabolic abnormalities, including elevated WC, high FPG, elevated BP, high TC level, high LDL-C, low HDL-C, or obesity, was associated with incident glaucoma.

It has been emphasized the importance of glaucoma screening and detecting in patients with metabolic syndrome and obesity, especially those with high blood pressure and high TGs.[40,43] Our results support the recommendation that patients with hypertriglyceridemia should undergo regular ophthalmological examinations to monitor the onset or progression of glaucoma.

In a recent meta-analysis, statin use was associated with a reduced incidence of glaucoma.[44] Experimental research has revealed that statins can increase aqueous outflow capacity by inducing cellular changes in trabecular meshwork structure.[45] The observational nature of our study does not allow us to evaluate whether interventions that lower TGs levels can modify glaucoma development and/or outcomes. Randomized clinical studies are needed to better investigate whether the use of triglyceride-lowering and / or cholesterol-lowering drugs may be useful in the prevention or risk reduction of glaucoma.

The strength of our study includes a comprehensive investigation of the causal relationship of metabolic risk factors and incident glaucoma through a population-based prospective longitudinal cohort study representative of the Chinese adult population. The nature of our study would establish the temporal sequence required for causal inference. In addition, the number of participants and the follow-up period in our study were sufficient to investigate the study question. We propose that the results of the study could be extrapolated to Chinese populations.

Our study has several limitations. First, as the included participants were 30 years or older, the results cannot be directly applied to younger patients. Second, gonioscopy was performed on 1 in 10 subjects as well

as those who were found to have LACD ≤40%, IOP >21 mm Hg, and those having a history of glaucoma or suspect. We could not identify the incident glaucomas to be angle closure glaucomas or open angle glaucomas in the analysis because not all the incident glaucoma subjects underwent gonioscopy. Hence, we were unable to investigate the associations between metabolic risk factors and the different subtypes of glaucoma. Third, metabolic syndrome components were defined using single lipid and glucose measurement, which may have biased the results. Fourth, among the included 5184 subjects, 702 of them had no blood sample obtained. The subjects with blood samples tended to be female, had larger BMI, larger WHR, and higher MBP, compared with those without blood samples. This could also cause a bias.

Conclusion

In summary, our study revealed that age and TGs level were independently associated with incident glaucoma. The data implied that hyperlipidemia be involved in the pathogenesis of glaucoma. Further research is needed to better understand the complex interactions among metabolic abnormalities, IOP, and the pathogenesis of glaucoma.

Acknowledgments

The authors thank all staff who contributed to this study.

Supported by research special fund of the Ministry of Health of the People's Republic of China (Grant Number 201002019). The funding organization had no role in the design or conduct of this research.

Disclosure: **Y. Zhang,** None; **Q. Zhang,** None; **R. Thomas,** None; **S.Z. Li,** None; **N.L. Wang,** None

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