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High HDL-C and high LDL-C are risk factors of pterygium in a population-based cross-sectional study in Southern China: the Dongguan Eye Study

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ABSTRACT

Objectives To investigate the relationship between serum lipids and pterygium in a large-scale rural population aged 40 years or older from Southern China.

Study design The Dongguan Eye Study was a cross-sectional population-based study from September 2011 to February 2012.

Setting The area was set in the rural area of Dongguan, Southern China.

Participants Adult rural population aged 40 or older.

Methods Participants underwent physical, haematological and ophthalmic examinations.

Primary and secondary outcome measures The frequency and risk factors of pterygium.

Results A total of 11 357 participants were eligible for inclusion and 8952 (78.8%) participants were enrolled for the systemic and ophthalmic examinations. The prevalence of pterygium was 17.3% after adjusting the sex and age distribution, 22.0% in participants with hypercholesterolaemia (total cholesterol ≥6.22 mmol/L (240 mg/dL)) and 21.8% in those with low-density lipoprotein-cholesterol (LDL-C) ≥4.14 mmol/L (160 mg/dL), respectively. After adjusting for multiple confounding factors, higher level of high-density lipoprotein-cholesterol (HDL-C) (OR: 1.23, 95% CI: 1.06 to 1.41) and LDL-C (OR: 1.13, 95% CI: 1.06 to 1.20) were positively associated with the risk of pterygium. The ORs for HDL-C or LDL-C with pterygium were significantly greater in participants aged 40–49 years than those aged 50 years or above (P for interaction <0.001). Furthermore, increased HDL-C showed greater association with pterygium in normal body mass index (BMI) group compared with overweight group (P for interaction=0.002).

Conclusion Increased HDL-C and LDL-C are risk factors of pterygium, especially in people <50 years or those with normal BMI level. Strict control of HDL-C and LDL-C may be a new prevention method in reducing the risk of pterygium.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A population-based design, a large sample size and the availability of multiple potential risk factors for pterygium.
⇒ This study explored the association between cholesterol and pterygium instead of the causality, thus further validation in longitudinal cohorts and experimental studies is necessary.
⇒ We only examined four main serum lipid indexes, other parameters like chylomicrons, very-low-density lipoprotein, intermediate-density lipoprotein, lipoprotein (a), apolipoprotein A1 and apolipoprotein B need further investigation to confirm their association with pterygium.

INTRODUCTION

Pterygium, one of the most common ocular disorders, is a wing-shaped fibrovascular tissue that protrudes from the bulbar conjunctiva towards to the cornea surface.[1] Patients may experience visual impairment due to irregular astigmatism, tear film abnormalities and direct encroachment onto the visual axis as disease progresses. A comprehensive meta-analysis reported that the prevalence of pterygium in 415 911 participants from 24 countries was 12%,the highest prevalence was 53% in China aged 40 years or older, and the lowest was 0.07% in Saudi Arabia aged 17 years or older.[2] Numerous epidemiological studies showed that male gender, older age, lower latitude, exposure to sunlight, outdoor occupations, living in a rural environment and lower level of education were risk factors for pterygium,[1–13] whereas wearing sunglasses and cigarette smoking were protective factors.[1 2 5 9] Although the definitive pathophysiology of pterygium is unclear, increasing evidence suggests that pterygium is a tumor-like proliferative disorder where cell growth and DNA replication are closely related to cholesterol metabolism and lipid peroxidation.[14–17]

Few studies have evaluated the relationship between pterygium and serum lipid and so far, the evidence is inconsistent. The

Singapore Malay Eye Study reported a positive association between grade 3 pterygium and serum total cholesterol (TC),[18] while no association between pterygium and TC was observed in a multiethnic Asian population.[12] A cross-sectional study in Han and Manchu ethnic populations in Hebei of China reported that higher high-density lipoprotein-cholesterol (HDL-C) was a risk factor of grade 2 or higher pterygium in males,[4] whereas retrospective case–control studies reported that pterygium had an inverse[19] or no association with HDL-C.[20] One case–control study showed that low-density lipoprotein-cholesterol (LDL-C) was significantly higher in patients with severe pterygium (grade 3),[20] yet no such study has ever been conducted among a large-scale population.

In this large-scale cross-sectional study, we utilised data from the Dongguan Eye Study (DES) to investigate the prevalence of pterygium and its association with serum lipid in a rural population from Southern China.

METHODS

Study population

The DES, a large population-based cross-sectional study in Southern China, was established to investigate the frequency and risk factors for visual impairment and major vision-threatening eye diseases in an adult rural population. The design and baseline characteristics of DES in detail were published previously.[21–23] In brief, residents aged 40 years or older from Hengli Town of Dongguan were recruited from September 2011 to February 2012. A total of 11 357 participants were eligible for inclusion and 8952 (78.8% of eligible) participants were successfully enrolled for systemic and ophthalmic examinations. Demographic socioeconomic status and health-related and vision-related quality of life data were collected during interviews.

Assessment of dyslipidaemia

Fasting venous blood was collected and laboratory tests were conducted, including triglyceride (TG), TC, HDL-C, LDL-C, fasting blood glucose (FBG) and haemoglobin A1c (HbA1c). All tests followed the manufacturers' instructions as described in Peng's report.[24] TG (glycerol phosphate oxidase-perioxidase aminopyrine method), TC (cholesterol oxidase-perioxidase aminopyrine method), HDL-C (direct method) and LDL-C (direct method) were measured using TBA-120 autoanalyzer (Toshiba Medical Systems, Japan). According to the Chinese guidelines on prevention and treatment of dyslipidaemia in adults, dyslipidaemia was defined as any of the following: TC ≥6.22 mmol/L (240 mg/dL, hypercholesterolaemia), LDL-C ≥4.14 mmol/L (160 mg/dL), HDL-C <1.04 mmol/L (40 mg/dL), TG ≥2.26 mmol/L (200 mg/dL, hypertriglyceridaemia) or a history of dyslipidaemia.[21 25]

Pterygium ascertainment

Pterygium was evaluated by two experience doctors (YC and QM) using the slit-lamp (IEC601-1, SL-1E, Topcon, Japan). The definition and grade of pterygium were used according to the Tanjong Pagar Survey and the Singapore Malay Eye Study.[10 18] Pterygium was defined as an extension of the conjunctiva onto the clear cornea for which there was no alternative explanation, such as inflammation or trauma. The three grades, based on relative transparency of pterygium tissue, were grade 1 (transparent), grade 2 (intermediate) and grade 3 (opaque). In a grade 1 pterygium, the episcleral vessels under the body were clearly visible, whereas a grade 3 pterygium completely obscured the episcleral vessels. All of the record of pterygium included which eye, which side, the morphologic feature and the length from the head to the limbus.[1 11] The record of pterygium included which eye, which side, the morphologic feature and the length from the head of pterygium to the limbus.

Covariate assessment

Height, weight, waist and hip circumference, heart rate and blood pressure were measured based on standardised protocol. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared, and was classified into three grades: underweight by less than 18.5 kg/m^2; normal range by 18.5 kg/m^2 to 24.9 kg/m^2; and overweight by equal or greater than 25 kg/m^2.[26] Body surface area (BSA) was calculated using the following formula: BSA (m^2)=0.0061 × height (cm) + 0.0124 × wt (kg) − 0.0099.

Statistical analysis

The crude prevalence of pterygium was described using prevalence and 95% CIs. Demographic and physical characteristics were presented as frequency (percentage) for categorical variables, and mean (SD) for continuous variables. To examine if a difference exists between pterygium and non-pterygium participants, we performed χ^2 tests for categorical data, and two sample t-tests for continuous variables as appropriate. The association between serum lipid and pterygium were analysed using logistic regression models. Parameters with p value <0.05 in the univariable analyses and other established risk factors for pterygium were adjusted in the models, and backward-conditional pattern was applied to filter the meaningful risk factors. To evaluate whether these relationships differ by pterygium risk factors, we did a subgroup analysis stratified by sex, age and BMI status those have been demonstrated to be involved in serum lipid.[27–29] Heterogeneity across subgroups was assessed using the likelihood ratio test, comparing the difference in fit statistics between models with a cross-product term of serum lipid and subgroup variable and those without that term. We performed all analysis using SPSS software (V.23.0; SPSS, Chicago, Illinois, USA). All statistical analyses were two-sided with a p value <0.05 indicating statistical significance.

Table 1 Prevalence of pterygium in the Dongguan Eye Study

	Number of total participants	Number of patients with pterygium	Prevalence % (95% CI)	P value
Total	8952	1619	18.1 (17.3 to 18.9)	
Sex				0.87
Male	3594	647	18.0 (16.7 to 19.3)	
Female	5358	972	18.1 (17.1 to 19.2)	
Age (years)				<0.001
40–49	3244	205	6.3 (5.5 to 7.2)	
50–59	2619	475	18.1 (16.7 to 19.6)	
60–69	1947	569	29.2 (27.2 to 31.2)	
70–79	828	276	33.3 (30.1 to 36.6)	
≥80	314	94	29.9 (24.8 to 35.0)	
TG (mmol/L)				0.22
<2.26	7392	1365	18.5 (17.6 to 19.4)	
≥2.26	1298	221	17.0 (15.0 to 19.1)	
TC (mmol/L)				<0.001
<6.22	7342	1289	17.6 (16.7 to 18.4)	
≥6.22	1348	297	22.0 (19.8 to 24.2)	
HDL-C (mmol/L)				0.36
<1.04	764	130	17.0 (14.3 to 19.7)	
≥1.04	7926	1456	18.4 (17.5 to 19.2)	
LDL-C (mmol/L)				0.003
<4.14	7721	1375	17.8 (17.0 to 18.7)	
≥4.14	969	211	21.8 (19.2 to 24.4)	

HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, serum total cholesterol; TG, triglycerides.

Patient and public involvement

Neither the patients nor the public were involved in this study. Each step in the study was verbally explained to the participants, and informed consent was obtained from each participant. If the participants could not know the consent statement because of vision loss or illiteracy, the consent was read by the interviewer.

RESULTS

Prevalence of pterygium in dyslipidaemia and normal population

Of the 8952 participants in the DES, there were 1619 (18.1%) participants with pterygium in either eyes and the standardised prevalence of pterygium was 17.3% corresponding to the sex and age distribution in the Guangdong Provincial population according to the census carried out in 2010.[30] No significant difference was observed between male and female (p=0.87). There was significant difference among each age group (p<0.001), with the highest prevalence in the 70–79-year-old group (table 1). Based on 8690 (97.1%) available serum lipid data, the prevalence of pterygium in participants with or without dyslipidaemia was further evaluated. The prevalence of pterygium was 22.0% in participants with hypercholesterolaemia and 21.8% in those with LDL-C ≥4.14 mmol/L (160 mg/dL), which was significantly higher than those with normal TC and normal LDL-C (p<0.001 and p=0.003, respectively). There was no significant difference in participants with and without abnormal TG and HDL-C (table 1).

Associations between serum lipid and pterygium

A total of 8400 (93.8% of participants) individuals with available data were involved in the univariate and multivariate analysis. Participants with pterygium had higher proportions of older age, farmer and lower level of education, had lower level of body height, body weight, BMI, BSA and hip circumference and had higher level of waist-to-hip ratio, mean SBP, TC, HDL-C, LDL-C, FBG and HbA1c (p<0.05) (table 2).

Table 3 shows three models for the association between the pterygium and serum lipid using multivariate binary logistic regression analysis. After adjusting for sex, age, occupation, level of education, history of smoking, BMI, mean SBP and FBG, higher prevalence of pterygium was independently associated with higher HDL-C (OR: 1.23, 95% CI: 1.06 to 1.41, p=0.005) and higher LDL-C (OR:

Table 2 Univariate analysis of the associations between pterygium and systemic parameters in the Dongguan Eye Study

Variables	Pterygium (n=1567) Number of persons (%) or Mean±SD	Non-Pterygium (n=6833) Number of persons (%) or Mean±SD	P value
Sex (male)	625 (39.9)	2757 (40.3)	0.74
Age	61.6±10.3	54.3±10.7	<0.001
Occupation (farmer)	877 (56.0)	3438 (50.3)	<0.001
Level of education			
Primary school and below	977 (62.3)	2766 (40.5)	<0.001
Junior school and above	590 (12.7)	4067 (87.3)	
History of smoking	396 (25.3)	1764 (25.8)	0.66
History of alcohol	122 (7.8)	473 (6.9)	0.23
Height (cm)	155.0±8.0	156.9±8.1	<0.001
Weight (kg)	58.6±10.8	61.0±11.1	<0.001
BMI (kg/m^2)	24.3±3.7	24.7±3.7	<0.001
BSA (m^2)	1.66±0.17	1.70±0.17	<0.001
Waist circumference (cm)	82.3±9.5	82.3±9.6	0.97
Hip circumference (cm)	92.7±7.0	93.9±7.1	<0.001
Waist-to-hip ratio	0.89±0.07	0.88±0.07	<0.001
Mean SBP (mm Hg)	137.4±20.2	132.9±19.0	<0.001
Mean DBP (mm Hg)	76.1±10.6	76.4±10.7	0.42
Mean heart rate (/minute)	79.9±12.3	80.2±12.6	0.41
TG (mmol/L)	1.54±1.37	1.58±1.34	0.27
TC (mmol/L)	5.35±1.06	5.23±1.02	<0.001
HDL-C (mmol/L)	1.54±0.39	1.49±0.40	<0.001
LDL-C (mmol/L)	3.14±0.93	3.04±0.91	<0.001
FBG (mmol/L)	5.89±1.49	5.79±1.51	0.02
HbA1c (%)	6.0±0.9	5.9±1.0	0.002

BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; TC, serum total cholesterol; TG, triglycerides.

Table 3 Multivariate analysis of the associations between pterygium and serum lipid in the Dongguan Eye Study

	Model 1			Model 2			Model 3		
Variables*	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Sex (male)	–	–	–	1.19	1.05 to 1.34	0.007	1.19	1.05 to 1.35	0.006
Age (years)	1.06	1.05 to 1.06	<0.001	1.05	1.05 to 1.06	<0.001	1.05	1.05 to 1.06	<0.001
HDL-C (mmol/L)	1.22	1.07 to 1.40	0.004	1.23	1.06 to 1.41	0.005	1.23	1.06 to 1.41	0.005
LDL-C (mmol/L)	1.11	1.05 to 1.18	0.001	1.12	1.06 to 1.20	<0.001	1.13	1.06 to 1.20	<0.001
Occupation (farmer)				1.35	1.20 to 1.51	<0.001	1.34	1.19 to 1.51	<0.001
Level of education (primary school and below)				1.49	1.31 to 1.70	<0.001	1.50	1.32 to 1.72	<0.001

Model 1: results from multivariate regression models adjusted for sex and age.
Model 2: further adjusted for occupation, level of education and history of smoking based on model 1.
Model 3: further adjusted for BMI, mean SBP and FBG based on model 2.
*TG, TC, history of smoking, BMI, mean SBP and FBG were no relationship with pterygium.
BMI, body mass index; FBG, fasting blood glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure.

Table 4 Effect of 1 mmol/L higher in HDL-C or LDL-C on the risk of pterygium

Subgroup	Number	HDL-C (per 1 mmol/L)		LDL-C (per 1 mmol/L)	
		Or (95% CI)	P for interaction	Or (95% CI)	P for interaction
Sex*			0.13		0.78
Male	3382	1.44 (1.11 to 1.89)		1.11 (1.00 to 1.22)	
Female	5018	1.11 (0.93 to 1.33)		1.14 (1.05 to 1.23)	
Age (years)†			<0.001		<0.001
40–49	3029	1.72 (1.21 to 2.44)		1.26 (1.06 to 1.48)	
≥50	5371	1.08 (0.92 to 1.27)		1.07 (1.00 to 1.14)	
BMI (kg/m^2)‡			0.001		0.14
18.5–24.9	4431	1.57 (1.27 to 1.94)		1.07 (0.98 to 1.17)	
≥25	3693	0.88 (0.67 to 1.14)		1.20 (1.09 to 1.31)	

*Adjusted for age, education level, occupation, history of smoking and BMI.
†Adjusted for sex, education level, occupation, history of smoking and BMI.
‡A total of 276 participants whose BMI <18.5 kg/m^2 were excluded in BMI subgroup analysis. Adjusted for sex, age, education level, occupation and history of smoking.
BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

1.13, 95% CI: 1.06 to 1.20, p<0.001), while there was no relationship with TC and TG. Moreover, male (OR: 1.19, 95% CI: 1.05 to 1.35), older age (OR: 1.05, 95% CI: 1.05 to 1.06), farmer occupation (OR: 1.34, 95% CI: 1.19 to 1.51) and lower level of education (OR: 1.50, 95% CI: 1.32 to 1.72) were also shown as risk factors of pterygium.

Given that serum lipid may be affected by sex, age and BMI level,[27–29] we examined the associations between serum lipid and pterygium stratified by these three variables. As shown in table 4, among participants aged 40–49 years, each 1 mmol/L increase in HDL-C and LDL-C was associated with 72% higher (OR: 1.72, 95% CI: 1.21 to 2.44) and 26% higher (OR: 1.26, 95% CI: 1.06 to 1.48) risk of pterygium, respectively. These associations were stronger than among participants aged 50 years or older. Moreover, a stronger positive association of HDL-C with pterygium was observed in participants with BMI between 18.5 kg/m^2 and 25 kg/m^2 (OR: 1.57, 95% CI: 1.27 to 1.94, p for interaction: 0.001).

We further analysed the association between the severity of pterygium and the level of serum lipid. The only influence factor between mild pterygium (grade 1 and grade 2) and severe pterygium (grade 3) was age (OR: 1.03, 95% CI: 1.02 to 1.04, p<0.001), which was obvious in the progression of pterygium. This result implied that the occurrence of pterygium, but not the severity, was related to serum lipid.

DISCUSSION

In this study, we found that the prevalence of pterygium was significantly greater in participants with higher TC and higher LDL-C, and higher HDL-C and higher LDL-C were positively associated with the risk of pterygium after adjusting for multiple confounding factors, especially in participants aged 40–49 years and those with normal BMI level. These data support the concept that alterations of cholesterol metabolism are involved in the development of pterygium[31] and suggest that high HDL-C and high LDL-C are risk factors of pterygium.

TG, TC, HDL-C and LDL-C are important constituents of the lipid fraction of human body and widely used for evaluating serum lipid. TC refers to the sum of all kinds of lipoprotein cholesterol in the blood, including HDL-C and LDL-C. LDL-C is generally parallel to TC, and HDL-C plays a role in cholesterol reverse transport.[25 28] Consequently, TC was excluded due to a possible multicollinearity between TC and HDL-C and LDL-C in the multiple regression models. However, if HDL-C and LDL-C were eliminated from the regression models, TC became a strong risk factor of pterygium (OR: 1.10, 95% CI: 1.04 to 1.16, p<0.001), which was consistent with the report by Cajucom-Uy *et al*.[18] The levels of TC, LDL-C and HDL-C are relatively stable and can be affected by age, sex, dietary habit and genetic factors,[28] which may in part explain the differences across studies. Our findings along with the significant increase in prevalence of dyslipidaemia in Chinese adults[28] have highlighted the importance of serum lipid on the development of pterygium.

Although evidence regarding the association of HDL-C with pterygium is limited, several studies provided insights into the role of HDL-C from an epidemiologic and mechanistic standpoint. A positive association of HDL-C with pterygium was observed in a cross-sectional study.[4] HDL-C has been associated with a number of eye diseases, such as early age-related macular degeneration[32–34] and diabetic retinopathy,[35] both of which shared the same risk factors (old age and sunlight exposure) and pathogenic mechanism (high levels of reactive oxygen intermediates and angiogenesis) with pterygium. HDL-C has been widely demonstrated to promote angiogenesis via interaction with hypoxia-inducible factor 1α (HIF-1α), the master regulator of angiogenic mediators,

and vascular endothelial growth factor (VEGF), a potent angiogenic mediator.[36–38] Our previous study showed that HIF-1α and VEGF increased dramatically in the conjunctiva epithelium of primary pterygium.[39] Similar results were obtained in the vascular endothelium and stromal cells of pterygium.[40–42] Furthermore, anti-VEGF drugs have been applied in the clinical setting as adjuvants for pterygium treatment and recurrence prevention.[43–45] Taken together, we speculate that HDL-C may be involved in the angiogenesis of pterygium via the HIF-1α/VEGF pathway.

To our knowledge, the present study is the first large-scale population-based study to report a positive association between LDL-C and pterygium. Plausible mechanisms exist to support the role LDL receptor (LDL-R) and its related protein in the pathogenesis of pterygium.[14 17 31 46 47] Peiretti and colleagues found hyperexpression of the LDL-R in primary pterygium.[14] Wu *et al* presented that the expression of LDL-R was positively correlated with the cells proliferation and the uptake of dil-LDL in subconjunctival fibroblasts coming from pterygium was higher than that from normal tissues.[47] Overexpression of LDL-R combined with excessive LDL may be attributed to the supplement of cholesterol for membrane synthesis which is associated with cellular proliferation. Moreover, the effectiveness of photodynamic therapy (PDT) with verteporfin for pterygium[48] and corneal neovascularisation[49 50] support the relation between cholesterol metabolism and the development of pterygium. Cellular uptake of verteporfin by means of LDL-R is necessary to achieve cytotoxic response to PDT.

Strengths of the current study include a population-based design, a large sample size and the availability of multiple potential risk factors for pterygium. However, the findings in this study should also be viewed with several limitations in mind. First, as a cross-sectional study, we only explored the association between cholesterol and pterygium instead of the causality, thus further validation in longitudinal cohorts and experimental studies is necessary. Second, we only examined four main serum lipid indexes, other parameters like chylomicrons, very-low-density lipoprotein, intermediate-density lipoprotein, lipoprotein (a), apolipoprotein A1 and apolipoprotein B need further investigation to confirm their association with pterygium.

In conclusion, higher HDL-C and higher LDL-C were positively associated with the development of pterygium, especially in participants <50 years or those with normal BMI level in the Southern China population. Our results suggest that strict control of the serum level of HDL-C and LDL-C may help in reducing the risk for pterygium. Further studies of pterygium with emphasis on cholesterol metabolism are warranted.

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Contributors SZ and YanleiC collected and managed the data, wrote the main manuscript. QM, YingC designed the study, collected the data and revised the main manuscript. HG, MZ, LixinZ, LiangZ, QL and JZ collected and managed the data. GZ and C-HL analysed and interpreted the data. All authors approved the manuscript. QM and YingC are responsible for the overall content as guarantors.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by The Medical Ethics Committee of Dongguan People's Hospital (ID.number: 2010-002); and the Research Ethics Committee of Guangdong Provincial People's Hospital (ID. Number: 2011028H) Participants gave informed consent to participate in the study before taking part. This study complied with the Declaration of Helsinki.

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