Coronary angiographic profile in Egyptian patients with xanthelasma palpebrarum

Noha Hassanin, Sameh Wadie Ghaly Bakhoum, Mahmoud Elsayed Saraya

Department of Cardiovascular Diseases, Cairo University, Cairo, Egypt

Correspondence to Noha Hassanin, MD, Assistant Professor of Cardiovascular Diseases, Cairo University, Egypt. Mob: +201000135742;
E-mail: Noha.Ali@kasralainy.edu.eg

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Background
Xanthelasma palpebrarum are yellow plaques that are found near the inner canthus of the eyelid. However, it is still controversial whether such lesions are marker for coronary artery disease.
Aim
The aim of the study was to investigate the association between xanthelasma and severity of coronary artery disease using coronary angiography.
Settings and design
A prospective, case–control study was conducted on 86 patients scheduled for coronary angiography to diagnose coronary artery disease. The study population included two groups. Groups A and B were formed of 43 patients each with and without xanthelasma, respectively.
Patients and methods
The day before diagnostic coronary angiography, all patients were subjected to full medical history taking; clinical examination; laboratory investigations, including lipoprotein (a) [Lp (a)], serum creatinine, and lipid profile; 12-lead electrocardiogram; and transthoracic echocardiography. A written informed consent was taken from all included patients, and approval of the CMREC (Cairo Medical Research Ethics Committee) was obtained.
Results
Waist circumferences were increased in patients with xanthelasma compared with those without. Low-density lipoprotein and Lp(a) levels were significantly increased in patients with xanthelasma. The severity of coronary artery disease was significantly increased in patients with xanthelasma.
Conclusion
Hypertension, diabetes, and dyslipidemia were common in patients with xanthelasma palpebrarum. The presence of xanthelasma and Lp(a) were independent predictors of coronary artery disease. The severity of coronary artery disease was significantly increased in patients with xanthelasma.

Keywords:
coronary angiography, coronary artery disease, xanthelasma palpebrarum

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Background

Xanthelasma palpebrarum (XP) are yellow plaques that are found near the inner canthus of the eyelid [1]. Xanthelasmata are formed of xanthoma cells, which are foamy histiocytes laden with intracellular fat deposits within the upper reticular dermis [2]. However, it is still controversial whether such lesions are a marker for atherosclerosis, coronary artery disease, insulin resistance, diabetes mellitus, hypertension, stroke, dyslipidemia, obesity, and hyperuricemia or not.

Dyslipidemia refers to total cholesterol more than 5.2 mmol/l, high-density lipoprotein-C less than 1.0 mmol/l (males) or less than 1.2 mmol/l (females), and triglycerides more than 1.7 mmol/l. However, decision making regarding the low-density lipoprotein (LDL)-C levels will depend on the patient's cardiovascular risk [3] (Table 1).

XP has an estimated incidence of 0.56–1.5% in Western countries. It is more common in women (32%) vs men (17.4%). The age of onset ranges from 15 to 73 years, with a peak incidence between 30 and 50 years [5].

Moreover, patients with XP have been seen to have lipid disorders; therefore, plasma lipid levels, including triglycerides, cholesterol, LDL and high-density lipoprotein, and apolipoprotein B100 levels, should be assessed. Different treatment options are available for XP, but none of them produce satisfactory results. Medical management involves lifestyle modifications

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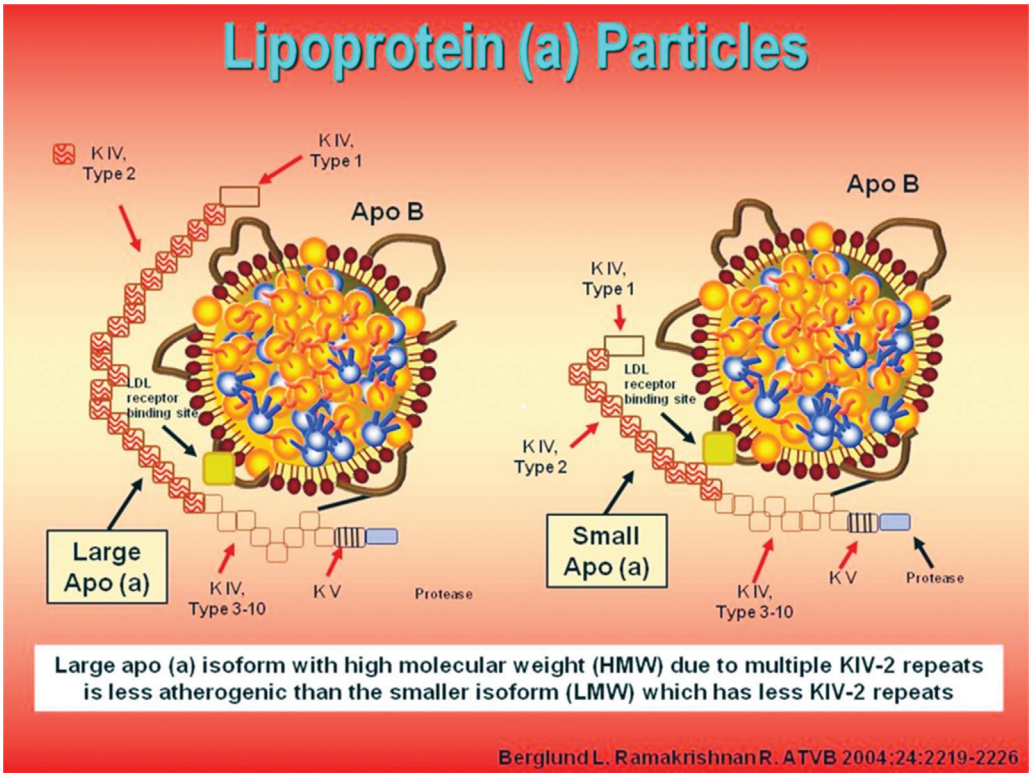
Table 1 Risk stratification of cardiovascular risk [4]

Very high-risk individuals are those with:
Established CVD
Diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidemia
GFR <30 ml/min/1.37 m^2 (stage 4)
High-risk individuals include:
Diabetes without target organ damage
CKD with GFR>or=30 to <60ml/min/1.37 m^2 (stage 3)
Very high levels of individuals risk factors (LDL-C>4.9 mmol/l, BP>180/110 mmHg)
Multiple risk factors that confer a 10-year risk for CVD>20% based on the Framingham Risk Score
Intermediate (moderate)-risk individuals:
Have a FRS–CVD score that considers a 10-year risk for CVD of 10–20%
Low-risk individuals:
Have a FRS–CVD score that considers a 10-year risk for CVD<10%

BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; FRS, Framingham risk score; GFR, glomerular filtration rate; LDL-C; low-density lipoprotein cholesterol.

Figure 1



Lipoprotein (a) particles [8].

such as regular physical exercise and low-fat diet in addition to lipid-lowering drugs.

Although important in the overall care of a patient with abnormal lipids, medical management has a limited role in the treatment of XP. Different surgical modalities for XP treatment are simple surgical excision, laser therapy, chemical cauterization with RF, and cryotherapy [6].

Lipoprotein (a): the Lp(a) structure is similar to that of LDL, in which a glycoprotein, apolipoprotein(a) [apo (a)], is covalently bound to apolipoprotein B (apoB) by a disulfide bridge, in a 1 : 1 molar ratio. Cholesterol content of Lp(a) and its density are similar to those of LDL particles. There is a strong inverse relationship between the size of Lp(a) and its serum levels, with smaller size correlating with higher serum levels. Smaller Lp(a) is associated with increased risks of cardiovascular disease (CVD) [7] (Fig. 1). Moreover, it was found that Lp(a) level less than 10.0 mg/dl is to be indicative of lower cardiovascular risk, with higher levels associated with an increase in cardiovascular risk [9].

The National Cholesterol Education Program for the Detection, Evaluation and treatment of hypercholesteremia in adult (NCEP-ATP III) found that higher levels of Lp(a) are associated with increased risk of cardiovascular events [10].

The primary goal of treatment of elevated Lp(a) is to lower LDL-C to the patient's target LDL-C level based on patient's risk category.

Studies suggest that the risk of CVD-associated elevated Lp(a) levels is higher in the presence of other CV risk factors including high LDL-C levels. Several studies showed that lowering LDL-C in the presence of high Lp(a) resulted in a reduction in CVD events [11]. Statins and bile acid sequestrates decrease LDL-C but lower Lp(a) only slightly. The new human monoclonal antibody to proprotein convertase subtilisin/kexin9 (PCSK9) is a protein that binds to LDL receptor (LDL-R). This complex is subjected to proteolytic degradation, thus preventing recycling of LDL-R to the cell surface [12]. Lipoprotein apheresis is the most effective way to lower Lp(a). Many studies have shown its lowering effect on serum lipids and Lp (a) as well as its safety [12].

Aim of the study was to compare coronary angiographic findings and Lp(a) in patients with and without xanthelasma who are already scheduled for coronary angiography to rule out coronary artery disease.

Patients and methods

The study was designed as a multicenter case–control comparative study conducted on 86 participants. The study population included patients with and without xanthelasma defined as groups A and B, respectively, who were scheduled for coronary angiography to rule out coronary artery disease (CAD).

The study was carried out at Cairo University Hospitals and National Heart Institute. A written informed consent was signed by all included patients and approval from the CMREC (Cairo Medical Research Ethics Committee) was taken.

Patients with serum creatinine above 2.0 mg/dl, females receiving oral contraception, any patient on current medication causing secondary hyperlipidemia, for example, corticosteroid, and patients experiencing acute coronary syndrome in the previous 2 months were excluded from the study. Hyperlipidemia was diagnosed if the total cholesterol level was 200 mg/dl or above and/or the LDL level was 130 mg/dl or above, or in patients receiving statin treatment [13].

In accordance with recent guidelines, it is recommended that hypertension be diagnosed when systolic blood pressure in the office or clinic is greater than or equal to 140 mmHg and/or diastolic blood pressure is greater than or equal to 90 mmHg following repeated examination [14].

Diabetes was diagnosed based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test [15].

All patients were subjected to full clinical examination, including general examination especially for presence of XP (unilateral or bilateral, single or multiple), waist circumference, local cardiac examination, 12-lead electrocardiogram, and transthoracic echocardiography.

Waist circumference was measured mid-way between the lower border of rib margin and the upper border of iliac crest with a nonelastic flexible tape. Measurements were taken while standing at the end of a normal expiration with a straight back, relaxed abdomen, and feet put together on a flat surface with minimal clothing. The tape used was held without any constricting force [16].

Lipoprotein (a) measurement

The Tina-quant Lipoprotein (a) Gen. 2 assay determines the concentration of Lp(a), rather than the mass of Lp(a). The measurement of the concentration provides a clear estimate of the number of Lp(a) particles independent of the molecular weight of the particle.

Diagnostic coronary angiography

Femoral sheath was introduced. CAD was defined as the presence of at least more than 50% stenosis of major coronary arteries (left anterior descending, left circumflex, or right coronary arteries) or their major branches (diagonal, obtuse marginal, posterior descending, or posterior left ventricular arteries). Femoral sheaths were removed after catheterization, with no residual hematomas.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, New York, USA). Continuous numerical data were presented as mean and SD, and intergroup differences were compared using the unpaired *t* test.

Categorical data were presented as ratio or number and percentage and intergroup differences were compared using Fisher's exact test. Ordinal data were compared using the χ^2 test for trend. Correlations were tested using the Pearson or Spearman rank correlation.

Results

Waist circumferences and age were significantly increased in patients with xanthelasma compared with those without (99.5±7.0 vs 94.0±8.9 cm, *P*=0.002, and 49.3±8.0 vs 45.3±4.2, *P*=0.005) (Table 2).

Blood pressure was significantly increased in patients with XP compared with those without (51.2 vs 16.3%, *P*=0.001). DM was prevalent in patients with XP compared with those without 12 (27.9%) vs 3 (7%) (*P*=0.021) (Table 3).

Lp(a) was significantly increased in patients with XP compared with those without (mean 33.6 vs 18.2, *P*=0.001) (Fig. 2).

Severity of CAD was significantly increased in patients with xanthelasma compared with those without [single-vessel disease: 9 (20.9%) vs 1 (2.3%), *P*=0.001; two-vessel disease 7 (16.3%) vs 0, *P*=0.001; three-vessel disease 13 (30.2%) vs 0, *P*=0.001; LMA 4 (9.3%) vs 0, *P*=0.001] (Table 4).

LMA disease was significant in patients with XP compared with those without (9.3%) vs 0, *P*=0.001). Lp(a) was strongly affected by serum creatinine, LDL, triglycerides, and total cholesterol (Table 5).

Multivariable binary logistic regression analysis for prediction of CAD revealed that xanthelasma (*P*=0.0001) and Lp(a) (*P*=0.007) were independent predictors of CAD at a cutoff point of 25.8.

Discussion

Lp(a) is a heterogenous macromolecule that was identified in 1963. High levels were found to be associated with myocardial infarction, CAD, and stroke [17].

Lp(a) has a strong homology with fibrinolytic enzyme plasminogen, and their genes are adjacent to each other on chromosome 6. It was suggested that it may exert its effect by competitively binding to plasminogen receptors and inhibiting fibrinolysis [18].

Table 2 Demographic characteristics of patients with or without xanthelasma

Variables	Group A: Xanthelasma (*n*=43)	Group B: non-Xanthelasma (*n*=43)	*P* value*
Age (years)	49.3±8.0	45.3±4.2	**0.005**
Waist circumference (cm)	99.5±7.0	94.0±8.9	**0.002**
Gender (M/F)	17/26	21/22	0.515

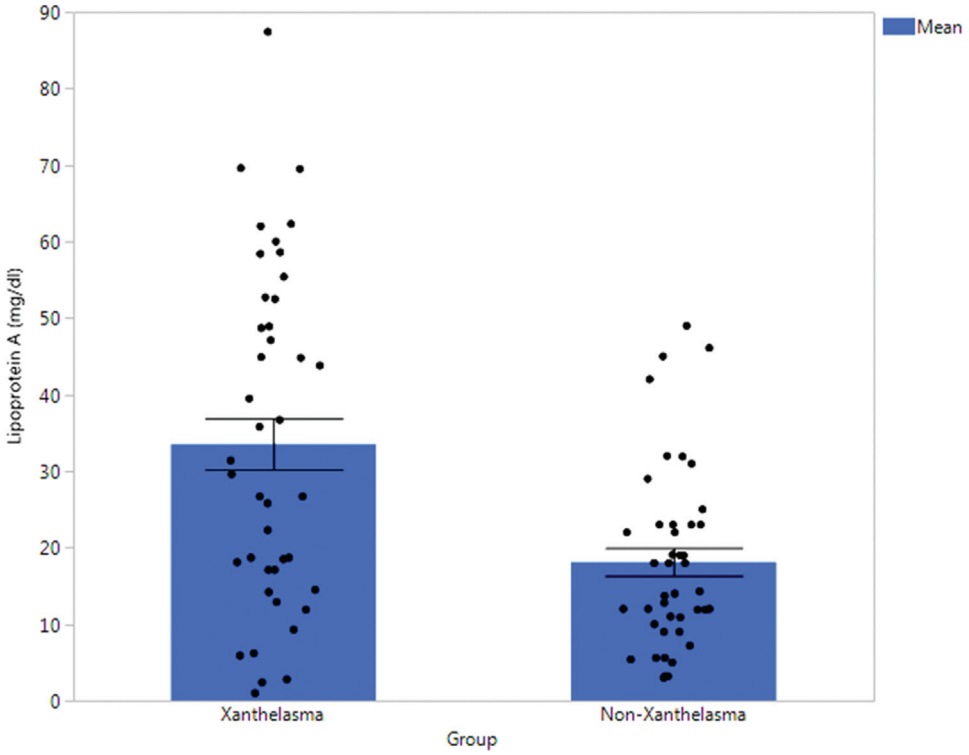
F, female; M, male.

Table 3 Prevalence of risk factors in patients with or without xanthelasma

Variables	Xanthelasma (*n*=43)	Non-Xanthelasma (*n*=43)	*P* value*
Hypertension			
Negative	21 (48.8)	36 (83.7)	**0.001**
Positive	22 (51.2)	7 (16.3)	
DM			
Negative	31 (72.1)	40 (93.0)	**0.021**
Positive	12 (27.9)	3 (7.0)	
Dyslipidemia			
Negative	13 (30.2)	34 (79.1)	<**0.001**
Positive	30 (69.8)	9 (20.9)	
Smoking			
Negative	23 (53.5)	24 (55.8)	1.000
Positive	20 (46.5)	19 (44.2)	
Family history of CAD			
Negative	26 (60.5)	36 (83.7)	**0.029**
Positive	17 (39.5)	7 (16.3)	
Family history of dyslipidemia			
Negative	19 (44.2)	29 (67.4)	0.050
Positive	24 (55.8)	14 (32.6)	

Data are number and percentage.CAD, coronary artery disease; DM, diabetes mellitus.

Figure 2



Mean lipoprotein (a) in patients with and without xanthelasma.

Table 4 Coronary angiographic findings in patients with or without xanthelasma

Variables	Xanthelasma (*n*=43)	Non-Xanthelasma (*n*=43)	*P* value
Coronary angiography			
Nil	10 (23.3)	42 (97.7)	<**0.001**
Single-vessel disease	9 (20.9)	1 (2.3)	
Two-vessel disease	7 (16.3)	0	
Three-vessel disease	13 (30.2)	0	
LMA disease	4 (9.3)	0	
CAD			
Negative	10 (23.3)	42 (97.7)	<**0.001**
Positive	33 (76.7)	1 (2.3)	
LMA disease			
Negative	39 (90.7)	43 (100.0)	0.116
Positive	4 (9.3)	0	

Data are number (n) and percentage ().CAD, coronary artery disease; LMA, left main artery.

The current study was designed as a multicenter, prospective, case–control, analytical study to assess relation between XP, Lp(a), and CAD.

The study population included two groups: A and B. Group A included 43 patients with clinical diagnosis of XP and on waiting list for coronary angiography. Group B included 43 patients without XP scheduled for preoperative coronary angiography.

Concordant with previous studies [19,20], we found that the prevalence of single-vessel, two-vessel, three-vessel disease and left main artery disease by coronary angiography was more prevalent in XP group.

LDL formed the majority of cholesterol entering xanthomas, which suggested that cholesterol accumulation is derived from blood [21].

Evaluation of the relationship between xanthelasma and hyperlipidemia has been emphasized in many studies [22].

These studies found that total cholesterol and LDL levels were higher in patients with xanthelasma than in

Table 5 Correlation between lipoprotein (a) and other numerical variables

Variables	Lipoprotein (a)	
	Pearson *r*	*P* value
Age	0.196	0.070
Waist circumference	0.125	0.252
Serum creatinine	**0.248**[*]	**0.021**
HDL	−0.162	0.137
LDL	**0.388**[**]	<**0.001**
TG	**0.312**[**]	**0.003**
Cholesterol	**0.579**[**]	<**0.001**

HDL, high-density lipoproteins; LDL, low-density lipoproteins; TG, triglycerides.[**]Correspondence to Correlation is significant at the 0.05 level (two-tailed).**Correlation is significant at the 0.01 level (two-tailed).

controls. The current study found that total cholesterol and LDL values were significantly higher in patients than in controls.

In agreement with previous studies [23–27], we demonstrated a significant correlation between Lp(a) and serum creatinine ($P<0.001$), LDL ($P<0.001$), triglycerides ($P<0.001$), total cholesterol, and severity of CAD ($P<0.001$).

Concordant with other studies [28,29], the current study using the multivariable binary logistic regression analysis for prediction of CAD revealed that XP ($P<0.0001$) and Lp(a) ($P0.007$) were independent predictors of CAD.

Conclusion

Severity of CAD was significantly increased in patients with xanthelasma compared with those without. Moreover, xanthelasma and Lp(a) were independent predictors of CAD.

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Conflicts of interest

There are no conflicts of interest.

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