ORIGINAL PAPER

Xanthelasma is not associated with increased risk of carotid atherosclerosis in normolipidaemia

C.-C. Chan,[1,2,3]* S.-J. Lin,[1,3]* J.-J. Hwang,[4,5] C.-C. Sun,[1] J.-S. Jeng,[6] B.-S. Hwang,[6] H.-C. Chiu,[1] M.-F. Chen,[5] C.-S. Liau,[5] H.-J. Hsu,[7] T.-C. Su[5,8]

SUMMARY

Objectives: Extracranial carotid artery (ECCA) atherosclerosis is well known to be associated with cardiovascular diseases. This study aims to investigate the difference of ECCA atherosclerosis between patients with xanthelasma and control subjects in normolipidaemia. **Methods:** Carotid atherosclerosis (CA) of 41 (8 males and 33 females) patients with xanthelasma and normolipidaemia, defined as levels of cholesterol below 6.21 mmol/l and triglyceride below 2.26 mmol/l, recruited from Department of Dermatology was compared with that of 85 age- and gender-matched control subjects. The extent and severity of CA were measured by high-resolution B-mode ultrasound and expressed as the mean intima-media thickness (IMT) of the common carotid artery (CCA) and ECCA plaque score. Mixed-effects model and multivariate logistic regression analyses were used to estimate the association between xanthelasma and CA. **Results:** Patients with xanthelasma showed significantly higher levels of low-density lipoprotein cholesterol (LDL-C) levels and higher body mass index (BMI) compared with the control group. Mixed models identified age, male gender, smoking and subjects of hypertension with medication, but not the presence of xanthelasma, were associated with an increase of CCA IMT. Multivariate logistic regression analysis revealed subjects of male gender, and hypertension with medication, but not the presence of xanthelasma, associated with thicker IMT, defined as IMT $\geq$ 75th percentile, or ECCA plaque score $\geq$ 3. **Conclusions:** Normolipidaemia with xanthelasma is not significantly associated with CA, but did relate with adverse cardiovascular profiles, such as higher BMI, waist circumference and LDL-C levels.

What's known

Xanthelasma associates with hyperlipidaemia. Hyperlipidaemia increases atherosclerosis. However, there is limited information regarding xanthelasma and cardiovascular disease.

What's new

Subjects of normolipidaemia with xanthelasma are not significantly associated with carotid atherosclerosis, but did relate with adverse cardiovascular profiles, such as higher BMI, waist circumference and LDL-C levels.

[1]Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[2]Department of Dermatology, Yu-Lin Branch of National Taiwan University Hospital, Douliu, Yulin, Taiwan
[3]Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan
[4]Department of Internal Medicine, Yu-Lin Branch of National Taiwan University Hospital, Douliu, Yu-Lin, Taiwan
[5]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[6]Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
[7]Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan
[8]Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan

Correspondence to:
Ta-Chen Su, MD, PhD,
Departments of Internal Medicine, and Environmental and Occupational Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, No. 7, Chung-Shan S. Road, Taipei, Taiwan
Tel.: + 886 2 23123456 (ext. 6719)
Fax: + 886 23712361
Email: tachensu@ntu.edu.tw

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The authors have declared that they have no interests which might be perceived as posing a conflict or bias.

*These two authors contributed equally to this work.

Introduction

Xanthelasma palpebrarum, or simply xanthelasma, is a commonly encountered cutaneous xanthoma with an unknown aetiology (1,2). They are diagnosed clinically with the presentation of oval or elongated yellowish plaques just beneath the skin of the periorbital region. Most commonly, they are noted near the inner canthus of the upper eyelid. About half of xanthelasma patients have been reported to have hyperlipidaemia (2), which is well known as a contributing factor of atherosclerotic vascular disease. Nevertheless, most patients, as well as medical doctors, put a value on cosmetic consultation without interest in the possible underlying disorders. Considering the possible clinical applications in preventive cardiology, the stigmata of xanthelasma could become a useful sign if it is significantly associated

with serum lipids, systemic atherosclerosis or other risk factors of major cardiovascular diseases (CVD).

Cardiovascular disease and stroke have been ranked among the leading causes of death in the past decades in the USA, Western world and also in Taiwan (3). Bodies of evidence support the importance of early detection of atherosclerosis and its associated risk factors in the prevention and treatment of atherosclerotic diseases. Common carotid artery (CCA), intima-media thickness (IMT) and extracranial carotid arteries (ECCA) atherosclerosis have been shown as having a significant association with cardiovascular risk factors, CVD and stroke (4–7). Measuring carotid atherosclerosis (CA) by ultrasound has been widely used for its simple and reliable detection of early preclinical atherosclerosis and for its high correlation between measured IMT and actual pathological changes (8,9).

As the association between xanthelasmas and CVD is still controversial (1,2,10–12), conducting a study to evaluate the relationship between this particular sign and the well-accepted surrogate outcome of CVD by CA seems to be valuable in a clinical setting. Because hyperlipidaemia, defined as cholesterol level ≥ 6.21 mmol/l (240 mg/dl) or triglyceride levels ≥ 2.26 mmol/l (200 mg/dl), has been well known to increase the risk of atherosclerosis. In this study, we used high-resolution carotid ultrasound to evaluate the ECCA atherosclerosis and IMT in patients of xanthelasma with normolipidaemia after controlling potential associated factors. Unlike most studies of xanthelasma and its association with major CVD (1,10–12), our cases were recruited from a general dermatology clinic rather than referrals from cardiovascular units. We investigated whether xanthelasmas provides suitable information to associate with subclinical atherosclerosis, as indexes by CA.

Subjects and methods

Study subjects

From 2001 through 2002, 63 (9 men and 54 women) consecutive patients diagnosed as xanthelasma palpebrarum were enrolled from a general dermatology clinic of National Taiwan University Hospital (NTUH). One hundred and twenty age- and gender-matched controls without xanthelasma (22 men and 98 women) were randomly recruited from subjects receiving physical examination during the same period in NTUH. Among 63 with xanthelasma palpebrarum, 41 (8 men and 33 women) patients were diagnosed as normolipidaemia, defined as levels of cholesterol below 6.21 mmol/l and triglyceride below 2.26 mmol/l. And, of the 120 age- and gender-matched controls, 85 (17 men and 68 women) fulfilled the criteria of normolipidaemia. Written informed consent was obtained from all participants. The study has been approved by the Ethics Committee of the Institutional Review Board of NTUH.

Assessment of cardiovascular risk factors

Blood pressure measurements were measured by a mercury sphygmomanometer in a standardised fashion, cuff size adjusted to the girth of the arm. Subjects with systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure higher than 90 mmHg, receiving antihypertensive medication (HTN-med), were considered hypertensive. Prevalent diabetes mellitus (DM) was defined as fasting glucose ≥ 6.99 mmol/l and/or a history of DM with management. Patients with poor control of DM (HbA1c $> 7.0\%$) were excluded. All participants did not have cholestasis, nephrotic syndrome or signifi-

cant evidence of familial hyperlipidaemia. Patients with cholesterol levels ≥ 6.21 mmol/l or triglyceride ≥ 2.26 mmol/l or on lipid-lowering agents were defined as hyperlipidaemia according to the criteria of the National Cholesterol Educational Program Adult Treatment Panel III (13). Body mass index (BMI) was computed from the subject's weight (in kilograms) over the square of height (in metres). We obtained data on smoking and alcohol drinking from a detailed chart review and a self-reported questionnaire for each patient.

As xanthelasma palpebrarum is a clinically diagnosed disease characterised by the presence of yellow, soft and either macular or slightly elevated plaques on the periocular skin, numbers and locations of xanthelasma palpebrarum were recorded on inspection by the same dermatologist in our study. The extent of xanthelasma status was arbitrarily classified into three categories: one single and xanthelasma size smaller than 2 cm^2, two or xanthelasma size over 2 cm^2, and three or more or xanthelasma area over 3 cm^2.

Overnight fasting (> 12 h) blood samples were collected for measurements of glucose, total cholesterol, high-density lipoprotein cholesterol and triglyceride by standard enzymatic methods with an automatic multichannel chemical analyser (Hitachi 7450, Hitachi Corp., Tokyo, Japan) in the central laboratory of NTUH. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula if their triglyceride levels < 4.52 mmol/l. If subjects' triglyceride levels ≥ 4.52 mmol/l, LDL were measured directly by enzymatic method with automatic chemical analyser.

ECCA ultrasonographic measurement

A Hewlett-Packard SONO 4500 ultrasound system (Andover, MA), equipped with a 3–11 MHz real-time B-mode scanner, was used for evaluation. Carotid end-organ disease was assessed by maximal IMT at carotid arteries and by ECCA plaque score. The measurement protocol for CA assessment has been described previously (4,5,14–18). The interobserver and intra-observer correlation coefficients were high (0.86–0.93 and 0.70–0.87 respectively) for both sides of CCA IMT measurements (16). Maximal IMT on the CCA proximal to the carotid bifurcation was obtained bilaterally. CCA1 and CCA2 are points located 0–1 and 1–2 cm, respectively, on the CCA distal from the carotid bifurcation. IMT of the posterior wall of the distal CCA was measured as the distance from the leading edge of the first echogenic line (interface between lumen and vascular intima) to the leading edge of the second line (interface between vascular media and adventitia). All the caro-

tid ultrasound examinations were performed by a experienced ultrasonographer (Hwang BS) and she was not aware of the health status and risk factors of the study individuals. For future and subsequent off-line analysis, all scans were recorded on super-Video Home System (VHS) videotape.

The plaque scoring quantified method has been described previously (4,5,14–18). To summarise briefly, a focal thickening of IMT with > 50% of thickness than the adjacent IMT was considered as an atherosclerotic plaque. A grade was assigned for each chosen segment: grade 0 for normal or no observable plaque, grade 1 for one small plaque with a diameter stenosis < 30%, grade 2 for one medium plaque with a 30–49% diameter stenosis or multiple small plaques, grade 3 for one large plaque with a 50–99% diameter stenosis or multiple plaques with at least one medium plaque and grade 4 for 100% occlusion. Carotid artery segments, including the proximal and distal CCA (> 20 and 0–20 mm distal to the bulb bifurcation respectively), bulb, internal carotid artery and external carotid artery, were examined bilaterally. The plaque score was calculated by summing the plaque grades at 10 segments of the ECCA. Reproducibility of the plaque grade scoring showed a good agreement with a kappa value of 0.70 (17).

Statistical analyses

Clinical features and cardiovascular risk factors of the study subjects were first compared by xanthelasma status, i.e. between patients with xanthelasma and controls, including all subjects and those subgroups of excluding of hyperlipidaemia respectively. Continuous variables were expressed as the mean ± 1 standard deviation. A *t*-test was used to make comparisons between these groups. For categorical data, a chi-squared test was used to test for the significance level between the two groups. The average CCA IMT measurements at CCA1 and CCA2 on both sides, and ECCA plaques were compared separately by xanthelasma and control groups, and the groups of extent of xanthelasma status.

The determinants of IMT (four measurements at different locations) of CCA were analysed by constructing mixed-effect regression models. The strength of associations between CA and xanthelasma and other potential risk factors was measured in terms of an odds ratio in the 95% confidence interval by using multivariate logistic regression analysis. A mean value of CCA IMT at or above the 75th percentile or ECCA score ≥ 3 was regarded as an indicator of significant CA. The statistical significance levels of alpha and beta were set at 5% and 20% respectively. Data analysis was performed with SAS

statistical software (version 8.2, SAS Institute Inc., Cary, NC).

Results

Table 1 shows the clinical features and cardiovascular risk factors between patients with xanthelasma and controls. No significant differences in the distributions of gender, age, and hypertension status, levels of blood pressure, prevalence of diabetes, and lifestyles were found between xanthelasma patients and control subjects. In comparison with control subjects, patients with xanthelasma had significantly higher levels of LDL-C, fasting glucose, waist circumference and higher average BMI (p < 0.05). After excluding subjects with hypercholesterolaemia and hypertriglyceridaemia, the difference of cholesterol levels is disappeared; however, the levels of LDL-C, BMI and waist circumference are still higher and a trend of higher glucose levels in patients with xanthelasma.

In Table 2, the average IMT measurements at different carotid locations were not significantly higher in patients with xanthelasma. There was no significant difference of ECCA score and the percentage with ECCA plaque between those patients with xanthelasma and control subjects. The number of the xanthelasma plaques and its association to carotid IMT and ECCA scores and plaque showed no significant difference, as shown in Table 3.

Mixed-effects model identified age, male gender, HTN-med and current smoking, but not the presence of xanthelasma, independent determinants of CCA IMT (Table 4). Subjects with DM and who had higher BMI or higher LDL-C had no significant association with CCA IMT. In Table 5, multivariate logistic regression models revealed that subjects with HTN-med and older age significantly increased the risk of thicker IMT. The risk of an ECCA plaque score ≥ 3 increased significantly in conjunction with subjects with HTN-med and male gender. However, xanthelasma was not a determinant for significant CA, indexes by thicker IMT or ECCA plaque score ≥ 3.

Discussion

This study is the first to demonstrate that normolipidaemia with xanthelasma is not significantly associated with subclinical atherosclerosis, in terms of CA. Subjects with HTN-med, male gender, older age and current smoking habit would have a higher CCA IMT. HTN-med and male gender were two important factors associated with a significant ECCA plaque scores. In this study, we found the number of xanthelasma was not related to thicker IMT at CCA,

Table 1 Basic characteristics of xanthelasma and matched control subjects

Characteristics	Xanthelasma (n = 63)	Control subjects (n = 120)	p-value	Xanthelasma with normolipidaemia (n = 41)	Control subjects with normolipidaemia (n = 85)	p-value
Age, years	50.78 (11.51)	50.06 (10.41)	0.777	52.49 (10.85)	51.22 (9.76)	0.513
Male	14.29%	18.33%	0.488	19.73%	21.18%	0.829
HTN	22.22%	16.67%	0.359	24.39%	16.47%	0.289
HTN-Med	17.46%	13.33%	0.455	19.51%	12.94%	0.334
SBP, mmHg	122.23 (23.29)	116.75 (17.00)	0.106	120.54 (17.07)	115.55 (15.43)	0.109
DBP, mmHg	73.36 (14.10)	74.452 (10.41)	0.593	71.95 (11.28)	73.26 (10.39)	0.527
DM	7.94%	3.33%	0.111	9.76%	3.53%	0.153
Glu, mmol/l	5.74 (1.78)	5.22 (0.54)	0.027	5.70 (1.66)	5.22 (0.57)	0.080
Smoking	17.46%	18.33%	0.884	17.07%	17.65%	0.937
Alcohol	6.35%	5.83%	0.249	7.32%	5.88%	0.757
CHO, mmol/l	6.02 (1.82)	5.29 (0.77)	0.003	5.13 (0.63)	4.99 (0.65)	0.279
LDL, mmol/l	3.81 (1.40)	3.00 (0.70)	< 0.000	3.24 (0.61)	2.81 (0.65)	0.001
HDL, mmol/l	1.34 (0.36)	1.42 (0.34)	0.132	1.33 (0.30)	1.39 (0.34)	0.293
TG*, mmol/l	1.12 (0.43–5.08)	1.04 (0.35–4.99)	0.266	1.03 (0.43–2.25)	0.98 (0.35–2.15)	0.450
BMI, kg/m^2	24.68 (4.40)	23.05 (2.90)	0.010	24.50 (3.17)	23.12 (2.94)	0.018
Waist, cm	81.43 (10.33)	77.85 (8.79)	0.021	83.78 (9.80)	78.02 (9.19)	0.002

HTN, hypertension; HTN-Med, on antihypertensive medication; SBP and DBP, systolic and diastolic blood pressure; DM, diabetes mellitus; Glu, glucose; CHO, cholesterol; LDL and HDL, low-density and high-density lipoprotein cholesterol; TG, triglyceride; BMI, body mass index. *Levels of TG were expressed as median (minimum–maximum) and analysed by two-sample paired (Wilcoxon) signed rank test.

Table 2 Measurements of common carotid artery (CCA), intima-media thickness (IMT) in different locations and extracranial carotid artery (ECCA) plaque scores, by xanthelasma status

	Xanthelasma (n = 41)	Control (n = 85)	p-value
IMT			
Rt CCA1, mm	0.63 (0.17)	0.64 (0.13)	0.683
Rt CCA2, mm	0.59 (0.14)	0.61 (0.12)	0.587
Rt CCA, mm	0.61 (0.15)	0.63 (0.11)	0.629
Lt CCA1, mm	0.65 (0.23)	0.64 (0.14)	0.817
Lt CCA2, mm	0.64 (0.17)	0.63 (0.12)	0.915
Lt CCA, mm	0.64 (0.19)	0.64 (0.12)	0.854
CCA, mm	0.63 (0.16)	0.63 (0.11)	0.907
*ECCA score	1.00 (2.19)	0.73 (1.29)	0.909
*ECCA plaque	34.15%	34.12%	0.998

Values in IMT are mean ± SD mm. CCA indicates mean IMT of both RCCA and LCCA. Values in ECCA score are average plaque score (mean ± SD). Values in ECCA plaque are per cent, showing the prevalence of ECCA plaque.
*Two-sample paired (Wilcoxon) signed rank test.

as well as higher ECCA plaque scores. The findings of the lack of relationship between the extent of xanthelasma and CA also supported that the presence of xanthelasma may not be at increased risk for atherosclerosis in normolipidaemia. However, the subjects of normolipidaemia with xanthelasma are related with adverse cardiovascular profiles, such as higher BMI, higher levels of LDL-C and glucose.

As in our previous studies, hypertension or hypertension with medication have been demonstrated as the major determinants of CCA IMT and significant CA (4,14,18). As our previous study (14), this study also applied a mixed regression model to associate multiple carotid IMT measures as repeated measurements with its risk factors, while previous studies have taken, on the whole, the average value of repeated IMT measurements (4–7). The rational use of mixed models assumes that repeated measurements have a random effect, which corresponds more to the bilateral measurements of IMT at a fixed specific segment for each subject. Statistically, it is generally more efficient than simply taking the mean and can possibly improve the detection power of limited study subjects. Furthermore, multivariate logistic regression analysis identified the similar risk factors (age and HTN-med) for a thicker IMT, and male gender and HTN-med for a significant ECCA plaque score.

Xanthelasma palpebrarum and its clinically significant association with hyperlipidaemia, along with impacts on atherosclerotic risk factors, have been widely discussed (1,2,10–12,19–22). Bergman authored two great reviews with regard to both clinical aspects, and ascribing the pathogenesis of this

Table 3 Extents of xanthelasma and common carotid artery (CCA) intima-media thickness (IMT) and extracranial carotid artery (ECCA) plaque scores

	Numbers of xanthelasma			
	1 n = 6	2 n = 24	≥ 3 n = 11	p-value, χ^2 for trend
IMT				
RCCA1, mm	0.71 (0.14)	0.62 (0.14)	0.60 (0.24)	0.4098
RCCA2, mm	0.66 (0.11)	0.60 (0.14)	0.53 (0.12)	0.1637
RCCA, mm	0.68 (0.11)	0.61 (0.14)	0.57 (0.18)	0.2846
LCCA1, mm	0.75 (0.20)	0.63 (0.12)	0.63 (0.39)	0.5123
LCCA2, mm	0.72 (0.18)	0.64 (0.13)	0.58 (0.24)	0.2562
LCCA, mm	0.74 (0.19)	0.64 (0.12)	0.61 (0.31)	0.4148
CCA, mm	0.71 (0.14)	0.62 (0.12)	0.59 (0.23)	0.3094
ECCA score	1.17 (1.47)	0.46 (0.93)	2.09 (3.75)	0.1197
ECCA plaque	50.00%	29.17%	36.36%	0.3684

Values in IMT are mean ± SD mm. RCCA indicates mean IMT of both RCCA1 and RCCA2; LCCA indicates mean IMT of both LCCA1 and LCCA2. Values in ECCA score are average plaque score. Values in ECCA plaque are per cent, showing the prevalence rate of ECCA plaque.

Table 4 Determinants of common carotid artery intima-media thickness by mixed-effects model

Characteristics	β (SE) mm
Intercept	0.57 (0.07)‡
Age, years, 10^{-2}	0.44 (0.21)*
Male gender	0.05 (0.02)†
Systolic BP, mmHg, 10^{-2}	0.00 (0.04)
Antihypertensive medication	0.06 (0.02)†
Diabetes mellitus	0.00 (0.03)
Smoking, current	0.06 (0.02)†
Body mass index, kg/m^2	0.02 (0.02)
LDL-cholesterol, mmol/l	−0.01 (0.01)
Xanthelasma, 10^{-2}	1.21 (1.30)
AIC	−596.0

p-value: *< 0.05, †< 0.01, ‡< 0.005. AIC, Akaike's information criterion; LDL, low-density lipoprotein; BP, blood pressure.

Table 5 Multivariate logistic regression models for carotid atherosclerosis

Characteristics	IMT ≥ 75th percentile OR (95% CI)	ECCA score ≥ 3 OR (95% CI)
Age, years	1.05 (1.00–1.12)*	1.04 (0.94–1.16)
Male gender	1.83 (0.56–5.98)	10.81 (1.76–66.31)†
Systolic BP, mmHg	1.01 (0.98–1.05)	1.01 (0.95–1.07)
Antihypertensive medication	4.67 (1.18–18.47)*	9.83 (1.32–73.13)*
Diabetes mellitus	0.35 (0.03–3.68)	0.69 (0.03–17.10)
Smoking, current	2.98 (0.90–9.90)	4.01 (0.62–26.15)
Body mass index, kg/m^2	0.89 (0.74–1.07)	0.85 (0.62–1.16)
LDL-cholesterol, mmol/l	0.97 (0.45–2.11)	3.33 (0.65–16.97)
Xanthelasma	1.14 (0.37–3.49)	1.23 (0.17–8.72)

Values are given as odds ratios (OR) (95% confidence intervals, CI). p-value: *< 0.05, †< 0.01. LDL, low-density lipoprotein; IMT, intima-media thickness; ECCA, extracranial carotid artery; BP, blood pressure.

particular skin presentation of xanthelasma, concluding that clinical value still could not be drawn as most investigators fail to demonstrate a study with appropriate control groups or are limited by small numbers of participants (1,2). Another important factor is due to biased patient selection, as most of the patients are collected from those who are visiting a cardiologist or had been sent for a cardiac evaluation, reflecting that these populations are predisposed to an association with cardiovascular morbidity and mortality (1,2,12,22).

To prevent similar limitations, our study chose xanthelasma patients from a dermatology outpatient clinic and excluded subjects of hyperlipidaemia, which was the major confounding factor that associated with atherosclerosis. Patients who visited for cosmetic consultation were less likely to be influenced by predisposing underlying cardiovascular disorders and were more likely to show their representatives among the general population. The control subjects were randomly selected from people visiting for a health examination and work-site health promotion programme during the same period.

Compared with the control group, subjects with xanthelasma have significantly higher levels of fasting glucose, serum LDL-C and BMI, which indicates some biological differences between these two groups. Elevated serum LDL-C in xanthelasma patients has been reported before (10,11,20,21). However, in this study, we are the first to report the elevated serum glucose level and higher BMI in subjects with xanthelasma. Higher levels of LDL and fasting glucose have been well documented as major cardiovascular risk factors (13). Obesity also was considered as a major cardiovascular risk factor by the American Heart Association (23). Although we did not show significant effects of these metabolic factors in the multivariate regression models in this study, the combination of poor metabolic profiles, higher levels of LDL, glucose and BMI in patients with xanthelasma, might contribute to adverse cardiovascular effects in the future.

This study is limited by its cross-sectional design. The fewer male participants in this study also indicated the cosmetic preference of women seeking for help in dermatologic clinic; however, may limit the gender inference. Although the data analysis failed to demonstrate a direct effect by xanthelasma to significant CA, other cardiovascular risk factors (age, male gender, HTN-med and smoking status) were significantly correlated with CCA IMT, and HTN-med and male gender associated with ECCA plaque score in this study, which were well in line with previous studies (4,5,13,17), which corroborated this study. This indicates that our design in elucidating the association between xanthelasma and atherosclerosis, although not significant enough to draw a conclusion, deserves our greater concern. Even though some traditional risk factors have been identified in association with xanthelasma in this study, conducting further study in genetic polymorphism for apolipoprotein E, B and other candidate genes might be necessary to answer the presentation of xanthelasma in some particular patients. All patients with xanthelasma should be reminded of the importance of regular checkup for blood cholesterol and receive HTN-med if with hypertension, and stop of smoking habit, which all have positive impacts in the emergence of atherosclerosis and long-term adverse effects on cardiovascular morbidity and mortality.

Acknowledgement

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