Article

Association of Xanthelasma palpebrarum (XP) with cardiovascular disease (CVD) risk factors

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Abstract: Xanthelasma palpebrarum (XP) is the most common cutaneous xanthoma occurs over or surrounding the eyelids in yellowish color and various shapes. The objective of this study was to describe the status of cardiovascular disease risk factors in XP patients and determine their association with XP. A case-control study was conducted among 81 cases (have XP) and 81 controls (no XP) among patients attended for cardiac check-up between January 2019 to July 2019 at Ad-Din Women's Medical College Hospital, Dhaka, Bangladesh. Among 162 subjects were interviewed in our study, majority were female (62.3%). XP were found more prevalent among female and several cardiac risk factors were significantly associated with XP. The chi-square analysis indicates gender (p=0.035), BMI (p=0.01), Angina history (p=0.008), and serum LDL (p=0.024) were significantly associated with presence of XP. A higher percentage of patients with high total serum cholesterol, TG levels, and LDL was observed in patients with XP in compared to control group. Our study reveals an increased presence of cardiovascular disease risk factors among patients with xanthelasma. Moreover, a statistically significant association of gender, BMI, angina history, and serum LDL with XP were observed.

Keywords: Xanthelasma palpebrarum; CVD; risk factors; Dhaka city

1. Introduction

Xanthelasma palpebrarum (XP) is a Xanthoma appeared as soft, velvety, yellowish papules and plaques of bilateral, symmetrical shaped over the eyelids (Akyüz *et al*., 2016; Oosterveer *et al*., 2009). In more than 100 years ago, Erasmus Wilson was first used the term xanthelasma (Kavoussi *et al*., 2016). Xanthelasma is originated from two Greek terms "xanthos" (yellow) and "elasma" (plate). Xanthelasma palpebrarum (XP) is the most recurrently seen cutaneous xanthoma. They are problematic as they have a common tendency of becoming larger, and become permanent (Jain et al., 2007; Özdöl et al., 2008; Pandhi *et al*., 2012).

Though the reason of xanthelasma development remains ambiguous, however, lipid abnormalities are deliberated as one of the predisposing factors (Wang *et al*., 2018). Histologically XP is constituted of foamy histiocytes with irregular Touton giant cells in the upper dermis layer. Ultrastructurally, the foamy histiocytes consist of cholesterol crystals and non-membrane bound lipid vacuoles (Pandhi *et al*., 2012; Wang *et al*., 2018).

The global incidence of Xanthelasma palpebrarum has been varied from 0.56% to 1.5% and the onset age ranges from 15 to 73 years. XP most commonly occurs in the fourth and fifth decade of individual life. According to many previously conducted epidemiological studies, XP is highly associated with atherosclerosis, cardiovascular disease, diabetes, obesity and pancreatitis (Dey, Aggarwal, & Dwivedi, 2013; Pandhi *et al*., 2012). A number of previously conducted research also identified increased biochemical lipid profiles for

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patients with XP such as, higher level of LDL and VLDL cholesterol and lower level of HDL cholesterol which are established predictors of cardiovascular diseases (Kavoussi *et al*., 2016).

Medical science suggests the control of lipid abnormalities via change in food habit, modifications in lifestyle, and medications those controls lipid level could aid in the resolution of XP (Wang *et al*., 2018). Some other ways such Surgery, chemical cautery, and laser therapy also suggested for the immediate treatment of XP (National CE, 2002).

Lipid-laden deposits of XP have been of wide interest among researchers and clinicians since long. Numerous studies have been conducted to find out the correlation between XP and cardiovascular diseases. However, it is still controversial whether XP are a marker for cardiovascular or metabolic disease or not. Therefore, our study was planned to address the variance in cardiovascular risk profile between Xanthelasma and non-Xanthelasma group; moreover, to find out the CVD risk factors those have significant association with XP.

2. Materials and Methods
2.1. Study sites
This study was conducted in the Department of Medicine/ Preventive Cardiology at Ad-Din Women's Medical College Hospital, Dhaka, Bangladesh.

2.2. Study design
Patients attending between January 2019 to July 2019 were screened, and 81 patients were found to have Xanthelasma palpebrarum (XP). XP in patients were identified by the presence of sharply demarcated yellow–orange plaques in their eyelids. The control group was constituted of 81 apparently normal individuals those attended the hospital for checkup to prevent cardiological problem.

2.3. Ethical approval
The Research Ethics Committee of Ad-Din Women's Medical College Hospital approved the study, and written informed consent was obtained from all of the participants.

2.4. Data collection
A standard questionnaire was used to collect information from the patient by face to face interview and diagnosis report for the evaluation of cardiac risk factors. Patients were interviewed regarding the presence of cardiovascular disease risk factors, such as smoking, hypertension, alcoholism, blood sugar level, lipid profile, previous history of cardiovascular disease, history of drug use, and xanthelasma. During the onset of interview, Blood pressure level, height, weight, of each of interview subject were measured and recorded appropriately. Body mass index (BMI) was calculated as weight divided by height square (kg/m^2). The blood samples were collected in the morning after an overnight fasting. Study participants were determined as hypertensive if they had>140 mmHg systolic blood pressure or a diastolic pressure > 90 mmHg or were taking any antihypertensive medicine. Participants had fasting blood glucose $\geq$ 126 mg/dl or taking any antidiabetic medication were determined as diabetic. If the participants had total cholesterol was > 200 mg/dl or taking medications, were considered as hyperlipidemic. Patients those are severely ill, had suffered from acute coronary syndromes in the last 2 months were excluded from the interview.

2.5. Data analysis
The collected data were entered in Microsoft XL (2013) and checked for consistency. Data were analyzed by SPSS 25 (IBM Corporation, USA) statistical package software. In our analysis $p<0.05$ was set as the value for statistical significance.

3. Results
We have conducted the study among 81 respondents with Xanthelasma palpebrarum (XP) and 81 appearently normal individuals and without XP. The average duration of XP among the study participants were 6.73 years with a standard deviation of 3.93. The both age and BMI was found higher among participants having XP in compared to participants without XP. The mean age and BMI of the study participants having XP was 50.15 and 27.534. On the other hand, mean age and BMI was 49.345 and 26.94 for participants not having XP (Table 1).

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Table 1. Comparison of Age and BMI between subjects with and without Xanthelasma palpebrarum (XP).

Variables	N	Minimum	Maximum	Mean	SD
Xanthelasma palpebrarum (Present)					
Age (year)	81	32	70	50.15	10.8
Duration of XP (year)	81	0.3	20	6.73	3.93
BMI	81	19.98	38.28	27.534	3.67
Xanthelasma palpebrarum (Absent)					
Age (year)	81	32	69	49.345	9.23
BMI	81	20.52	40.34	26.94	3.999

Overall 161 subjects were interviewed in our study where majority were form middle aged group (59.9%) and 62.3% of the participants were female. However, among the cases the percentage of female were even higher (70.4%). A high percentage of overweight (43.8%) and obesity (21.6%) were observed and among the cases the percentage of overweight was relatively high (55.6%) compared to normal or obese individuals. High prevalence of diabetes (42.0%) and Hypertension (53.1%) were observed among the cases, which were visibly higher than the control group. Family history of heart disease (49.4%) was very common among the case group and relatively higher than the control group (42.0%).

Among the cases we found higher percentage of patients with high total serum cholesterol (hyperlipidemia), high serum TG levels, and high serum LDL in compared to control group. However, wide variance was not observed in the HDL among cases and control group (Table 2).

Table 2. Comparison of clinical and laboratory characteristics between subjects with and without xanthelasma.

Variable	Category	Overall Frequency (%)	Cases (XP) Frequency (%)	Controls (No XP) Frequency (%)
Age	30-50 years	97 (59.9)	46 (56.8)	51 (63.0)
	51-70 years	65 (40.1)	35 (43.2)	30 (37.0)
Gender	Female	101 (62.3)	57 (70.4)	44 (54.3)
	Male	61 (37.7)	24 (29.6)	37 (45.7)
BMI type	Normal	56 (34.6)	21 (25.9)	35 (43.2)
	Obese	35 (21.6)	15 (18.5)	20 (24.7)
	Overweight	71 (43.8)	45 (55.6)	26 (32.1)
Diabetes	No	97 (59.9)	47 (58.0)	50 (61.7)
	Yes	65 (40.1)	34 (42.0)	31 (38.3)
Hypertension	No	82 (50.6)	38 (46.9)	44 (54.3)
	Yes	80 (49.4)	43 (53.1)	37 (45.7)
Physical exercise	Irregular	95 (58.6)	51 (63.0)	44 (54.3)
	Don't	47 (29.0)	18 (22.2)	29 (35.8)
	Regular	20 (12.3)	12 (14.8)	8 (9.9)
Smoking	No	128 (79.0)	63 (77.8)	65 (80.2)
	Yes	34.0 (21.0)	18 (22.2)	16 (19.8)
Family history of heart disease	No	88 (54.3)	41 (50.6)	47 (58.0)
	Yes	74 (45.7)	40 (49.4)	34 (42.0)
Hormone replacement therapy	No	157 (96.9)	78 (96.3)	79 (97.5)
	Yes	5 (3.1)	3 (3.7)	2 (2.5)
Alcoholism	No	155 (95.7)	79 (97.5)	76 (93.8)
	Yes	7 (4.3)	2 (2.5)	5 (6.2)
Angina history	No	138 (85.2)	63 (77.8)	75 (92.6)
	Yes	24 (14.8)	18 (22.2)	6 (7.4)
Acute coronary syndrome history	No	155 (95.7)	76 (93.8)	79 (97.5)
	Yes	7 (4.3)	5 (6.2)	2 (2.5)
Right ventricular tachycardia (RVT) history	No	159 (98.1)	80 (98.8)	79 (97.5)
	Yes	3 (1.9)	1 (1.2)	2 (2.5)
Ischemic stroke history	No	157 (96.9)	78 (96.3)	79 (97.5)
	Yes	5 (3.1)	3 (3.7)	2 (2.5)
Hyperlipidemia	High	93 (57.4)	49 (60.5)	44 (54.3)

	Normal	69 942.6)	32 (39.5)	37 (45.7)
Serum TG	High	82 (50.6)	45 (55.6)	37 (45.7)
	Normal	80 (49.4)	36 (44.4)	44 (54.3)
Serum HDL	High	13 (8.0)	11 (13.6)	15 (18.5)
	Low	39 (24.1)	13 (16.0)	13 (16.0)
	Normal	110 (67.9)	57 (70.4)	53 (65.4)
Serum LDL	High	60 (37.0)	36 (44.4)	24 (29.6)
	Normal	102 (63.0)	45 (55.6)	57 (70.4)
TG: Triglyceride; HDL: High density lipoprotein; LDL: Low-density lipoprotein				

We have conducted the unadjusted analysis using chi square test (Table 3). Our study identified gender (Chi-square: 4.4; p=0.035), BMI (Chi-square: 9.29; p=0.01), Angina history (Chi-square: 7.04; p=0.008), and serum LDL (Chi-square: 5.121; p=0.024) were significantly associated with presence of XP. The 95% Ionfidence Interval (CI) of Odds Ratio also defines gender, BMI, Angina, and LDL as significant predictors for XP as they don't contain null value 1. Odds ratio also indicates, males are 50% less likely to develop XP in compared to female. Participants having history of angina had 3.57 times higher prevalence of XP and having serum LDL of normal decrease 52% risk of having XP.

Table 3. Unadjusted analysis (chi-square) of Xanthelasma palpebrarum (XP) and cardiovascular disease risk factors.

Variable	Category	Xanthelasma		Chi-square	OR (95% CI)	P value
		Yes	No			
Age	30-50 years	46	51	0.642	1.29 (0.69-2.43)	0.42
	51-70 years	35	30			
Gender	Female	57	44	4.44	0.50 (0.26-0.95)	0.035*
	Male	24	37			
BMI type	Normal	21	35	9.29		0.01*
	Obese	15	20			
	Overweight	45	26			
Diabetes	No	47	50	0.23	1.16 (0.62-2.18)	0.63
	Yes	34	31			
Hypertension	No	38	44	0.89	1.35 (0.73-2.49)	0.35
	Yes	43	37			
Physical exercise	Irregular	51	44	3.89		0.14
	Don't	18	29			
	Regular	12	8			
Smoking	No	63	65	0.15	1.16 (0.55-2.47)	0.70
	Yes	18	16			
Family history of heart disease	No	41	47	0.89	1.35 (0.73-2.50)	0.34
	Yes	40	34			
Hormone replacement therapy	No	78	79	0.21	1.52 (0.25-9.34)	0.65
	Yes	3	2			
Alcoholism	No	79	76	1.34	0.39 (0.08-2.04)	0.25
	Yes	2	5			
Angina history	No	63	75	7.04	3.57 (1.34-9.54)	0.008*
	Yes	18	6			
ACS history	No	76	79	1.35	2.59 (0.49-13.80)	0.24
	Yes	5	2			
RVT history	No	80	79	0.34	0.49 (0.05-5.55)	0.56
	Yes	1	2			
Ischemic stroke history	No	78	79	0.21	1.52 (0.25-9.34)	0.65
	Yes	3	2			
Serum total cholesterol	High	49	44	0.63	0.78 (0.42-1.45)	0.43
	Normal	32	37			
Serum TG	High	45	37	1.58	0.67 (0.36-1.24)	0.21
	Normal	36	44			
Serum HDL	High	11	15	0.761		0.68
	Low	13	13			
	Normal	57	53			
Serum LDL	High	38	24	5.121	0.48 (0.25-0.91)	0.024*
	Normal	43	57			
*P < 0.05 or statistically significant association; OR: Odds Ratio, CI: Confidence Interval						

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The statistically significant variables of our unadjusted analysis were subjected to multiple logistic regression model. All of the variables except serum LDL remain significant in our adjusted model (Table 4).

Table 4. Adjusted analysis of significant determinants Xanthelasma palpebrarum (XP) using multiple logistic regression analysis.

Variable	Category	Estimate	AOR (95% CI)	Significance
	Male	Reference	Reference	Reference
BMI type	Normal	-0.998	0.369 (0.168-0.810)	0.013*
	Obese	-1.084	0.338 (0.137-0.834)	0.019*
	Overweight	Reference	Reference	Reference
Angina history	No	-1.337	0.263 (0.090-0.763)	0.014*
	Yes	Reference	Reference	Reference
Serum LDL	High	0.599	1.820 (0.893-3.710)	0.09
	Normal	Reference	Reference	Reference
*P < 0.05 or statistically significant association; AOR: Adjusted Odds Ratio, CI: Confidence Interval				

4. Discussion

Our case-control study was sought to find out the association between Xanthelasma palpebrarum (XP) and cardiac risk factors. A validated questionnaire was used to collect information from the respondents. The both age and BMI were found higher among participants with XP in compared to participants without XP. Both of our unadjusted and adjusted model revealed significant association between presence of XP and higher BMI. A number of studies previously conducted also revealed the association between Xanthelasma and BMI (Akyüz *et al*., 2016; Chen *et al*., 2017; Dwivedi *et al*., , 2012). Most of previously conducted study observed that XP is more prevalent among women in compared to men. We identified higher prevalence of XP among female and a statistically significant association were observed. The adjusted analysis indicates, the prevalence of XP is 2.5 times higher among female than male (Kavoussi *et al*., 2016; Nair *et al*., 2016).

In compared to the control group, higher prevalence of diabetes and Hypertension were observed among XP patients, which were higher than the control group. However, there was no statistically significance association were observed between XP and diabetes, hypertension. Our study is in line with the previously conducted studies in India (Pandhi *et al*., 2012).

Most of the cardiac risk factor studied in our research is relatively common among the XP group such as family history of heart disease, hormone replacement therapy. We have observed higher percentage of hyperlipidemia, high serum TG levels, and high serum LDL among XP patients in compared to control group. However, wide variance was not observed in the HDL among cases and control group. These findings are corroborated with the previously conducted studies in India (Sharma *et al*., 2013) and China (Li *et al*., 2017).

A statistically significant association were also observed between having the previous history of angina and XM in both of our adjusted and unadjusted analysis which is also supported by a number of previously conducted studies (Kul and Akyüz, 2018; Christoffersen *et al*., 2011).

5. Conclusions

Our study revealed significant association of several cardiovascular disease risk factors (Sex, BMI, Angina history, LDL level) with Xanthelasma palpebrarum. Which is in line with most of the previously conducted studies and reconfirms the association of cardiovascular disease and Xanthelasma palpebrarum. Our study may play significant role in control of cardiovascular disease and increase the awareness on Xanthelasma palpebrarum.

Conflict of interest

None to declare.

References

Akyüz AR, MT Ałaç, T Turan, S Şahin, S Kul, L Korkmaz and Ş Çelik, 2016. Xanthelasma is associated with an increased amount of epicardial adipose tissue. Med. Prin. Pract., 25: 187–190.

Chen Y, XJ He, MJ Zhou and YM Li, 2017. Gastric xanthelasma and metabolic disorders: a large retrospective study among Chinese population. World J. Gastroenterol., 23: 7756–7764.

Dey A, R Aggarwal and S Dwivedi, 2013. Cardiovascular profile of xanthelasma palpebrarum. BioMed Research International, 2013. https://doi.org/10.1155/2013/932863

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Dwivedi S, A Aggarwal, S Singh and V Sharma, 2012. Familial xanthelasma with dyslipidemia: just another family trait? N. Am. J. Med. Sci., 4: 238–240.

Jain A, P Goyal, PK Nigam, H Gurbaksh and RC Sharma, 2007. Xanthelasma palpebrarum-clinical and biochemical profile in a tertiary care hospital of Delhi. Indian J. Clin. Biochem., 22: 151–153.

Kavoussi H, A Ebrahimi, M Rezaei, M Ramezani, B Najafi and R Kavoussi, 2016. Serum lipid profile and clinical characteristics of patients with xanthelasma palpebrarum. Anais Brasileiros de Dermatologia, 91: 468–471.

Kul S and AR Akyüz, 2018. Xanthelasma Palpebrarum Artmış Nötrofil/Lenfosit ve Platelet/Lenfosit Oranı ile İlişkilidir. Sakarya Med. J., 8: 63–69.

Li X, A Wang, J Wang, J Wu, D Wang, X Gao and X Zhao, 2017. Association between high-density-lipoprotein-cholesterol levels and the prevalence of asymptomatic intracranial arterial stenosis. Sci. Rep., 7: 573.

Christoffersen M, R Frikke-Schmidt, P Schnohr, GB Jensen, BG Nordestgaard and A Tybjærg-Hansen, 2011. Xanthelasmata, arcus corneae, and ischaemic vascular disease and death in general population: Prospective cohort study. BMJ, 343:d5497.

Nair PA, CR Patel, JD Ganjiwale, NG Diwan and NB Jivani, 2016. Xanthelasma palpebrarum with arcus cornea: A clinical and biochemical study. Indian J. Dermatol., 61: 295–300.

National CE, 2002. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. Circulation, 106: 3143-421.

Oosterveer DM, J Versmissen, M Yazdanpanah, TH Hamza and EJG Sijbrands, 2009. Differences in characteristics and risk of cardiovascular disease in familial hypercholesterolemia patients with and without tendon xanthomas: A systematic review and meta-analysis. Atherosclerosis, 207: 311–317.

Özdöl S, S Şahin and L Tokgözoğlu, 2008. Xanthelasma palpebrarum and its relation to atherosclerotic risk factors and lipoprotein (a). Int. J. Dermatol., 47: 785–789.

Pandhi D, P Gupta, A Singal, A Tondon, SB Sharma and SV Madhu, 2012. Xanthelasma palpebrarum: A marker of premature atherosclerosis (risk of atherosclerosis in xanthelasma). Postgrad. Med. J., 88: 198–204.

Sharma P, D Patgiri, G Sharma and MS Pathak, 2013. Serum lipid profile in Xanthelasma Palpebrum. Indian J. Basic Appl. Med. Res., 7: 732–737.

Wang KY, KC Hsu, WC Liu, KC Yang and LW Chen, 2018. Relationship Between Xanthelasma Palpebrarum and Hyperlipidemia. Ann. Plast. Surg., 80: S84–S86.