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
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/m²). 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 ≥ 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 apparently 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).
Table 1. Comparison of Age and BMI between subjects with and without Xanthelasma palpebrarum (XP).

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

Overall 161 subjects were interviewed in our study where majority were from 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                              | 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)         | 44 (52.0)                | 31 (38.3)                      |
| Hypertension                          | No 82 (50.6)          | 43 (53.1)                | 37 (45.7)                      |
|                                       | Yes 80 (49.4)         | 43 (55.9)                | 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)                      |
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 |
|------------------------------|-------------------|-------------|------------|-------------|---------|
| Age                          | 30-50 years       | Yes: 46     | 0.642      | 1.29 (0.69-2.43) | 0.42    |
|                              |                   | No: 51      |            |             |         |
|                              | 51-70 years       | Yes: 35     |            |             |         |
|                              |                   | No: 30      |            |             |         |
| Gender                       | Female            | Yes: 57     | 4.44       | 0.50 (0.26-0.95) | 0.035*  |
|                              |                   | No: 44      |            |             |         |
|                              | Male              | Yes: 24     |            |             |         |
|                              |                   | No: 37      |            |             |         |
| BMI type                     | Normal            | Yes: 21     | 9.29       |             | 0.01*   |
|                              |                   | No: 35      |            |             |         |
|                              | Obese             | Yes: 15     |            |             |         |
|                              |                   | No: 20      |            |             |         |
|                              | Overweight        | Yes: 45     |            |             |         |
|                              |                   | No: 26      |            |             |         |
| Diabetes                     | No                | Yes: 47     | 0.23       | 1.16 (0.62-2.18) | 0.63    |
|                              |                   | No: 34      |            |             |         |
|                              | Yes               | Yes: 50     |            |             |         |
|                              |                   | No: 31      |            |             |         |
| Hypertension                 | No                | Yes: 38     | 0.89       | 1.35 (0.73-2.49) | 0.35    |
|                              |                   | No: 44      |            |             |         |
|                              | Yes               | Yes: 43     |            |             |         |
|                              |                   | No: 37      |            |             |         |
| Physical exercise            | Irregular         | Yes: 51     | 3.89       |             | 0.14    |
|                              |                   | Yes: 44     |            |             |         |
|                              | Regular           | Yes: 12     |            |             |         |
|                              |                   | No: 8       |            |             |         |
| Smoking                      | No                | Yes: 63     | 0.15       | 1.16 (0.55-2.47) | 0.70    |
|                              |                   | Yes: 65     |            |             |         |
|                              | Yes               | Yes: 18     |            |             |         |
|                              |                   | No: 16      |            |             |         |
| Family history of heart disease | No                | Yes: 41     | 0.89       | 1.35 (0.73-2.50) | 0.34    |
|                              |                   | No: 47      |            |             |         |
|                              | Yes               | Yes: 40     |            |             |         |
|                              |                   | No: 34      |            |             |         |
| Hormone replacement therapy  | No                | Yes: 78     | 0.21       | 1.52 (0.25-9.34) | 0.65    |
|                              |                   | No: 79      |            |             |         |
|                              | Yes               | Yes: 3      |            |             |         |
|                              |                   | No: 2       |            |             |         |
| Alcoholism                   | No                | Yes: 79     | 1.34       | 0.39 (0.08-2.04) | 0.25    |
|                              |                   | Yes: 76     |            |             |         |
|                              | Yes               | Yes: 2      |            |             |         |
|                              |                   | No: 5       |            |             |         |
| Angina history               | No                | Yes: 63     | 7.04       | 3.57 (1.34-9.54) | 0.008*  |
|                              |                   | No: 75      |            |             |         |
|                              | Yes               | Yes: 18     |            |             |         |
|                              |                   | No: 6       |            |             |         |
| ACS history                  | No                | Yes: 76     | 1.35       | 2.59 (0.49-13.80) | 0.24    |
|                              |                   | No: 79      |            |             |         |
|                              | Yes               | Yes: 5      |            |             |         |
|                              |                   | No: 2       |            |             |         |
| RVT history                  | No                | Yes: 80     | 0.34       | 0.49 (0.05-5.55) | 0.56    |
|                              |                   | No: 79      |            |             |         |
|                              | Yes               | Yes: 1      |            |             |         |
|                              |                   | No: 2       |            |             |         |
| Ischemic stroke history      | No                | Yes: 78     | 0.21       | 1.52 (0.25-9.34) | 0.65    |
|                              |                   | No: 79      |            |             |         |
|                              | Yes               | Yes: 3      |            |             |         |
|                              |                   | No: 2       |            |             |         |
| Serum total cholesterol      | High              | Yes: 49     | 0.63       | 0.78 (0.42-1.45) | 0.43    |
|                              |                   | No: 44      |            |             |         |
|                              | Normal            | Yes: 32     |            |             |         |
|                              |                   | No: 37      |            |             |         |
| Serum TG                     | High              | Yes: 45     | 1.58       | 0.67 (0.36-1.24) | 0.21    |
|                              |                   | No: 37      |            |             |         |
|                              | Normal            | Yes: 36     |            |             |         |
|                              |                   | No: 44      |            |             |         |
| Serum HDL                    | High              | Yes: 11     | 0.761      |             | 0.68    |
|                              |                   | No: 15      |            |             |         |
|                              | Low               | Yes: 13     |            |             |         |
|                              |                   | No: 13      |            |             |         |
|                              | Normal            | Yes: 57     |            |             |         |
|                              |                   | No: 53      |            |             |         |
| Serum LDL                    | High              | Yes: 38     | 5.121      | 0.48 (0.25-0.91) | 0.024*  |
|                              |                   | No: 24      |            |             |         |
|                              | Normal            | Yes: 43     |            |             |         |
|                              |                   | No: 57      |            |             |         |

*P < 0.05 or statistically significant association; OR: Odds Ratio, CI: Confidence Interval

TG: Triglyceride; HDL: High density lipoprotein; LDL: Low-density lipoprotein
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 |
|----------------|--------------|----------|----------------------|--------------|
| BMI type       | Male Reference | -0.998   | 0.369 (0.168-0.810)  | 0.013*       |
|                | Normal        | Reference| Reference            | Reference    |
|                | 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.

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