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Original Article

Lipid profile and carotid intima–media thickness in xanthelasma palpebrarum: A case–control study in Northeast India

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ABSTRACT

Background: Xanthelasma palpebrarum (XP) is a common cutaneous xanthoma often associated with dyslipidemia. Carotid intima–media thickness (CIMT) is a non-invasive method of monitoring subclinical atherosclerotic plaque formation and its progression. This study was conducted to assess the cardiovascular comorbidities in patients with XP by measuring the CIMT and serum lipid profile. **Materials and Methods:** A total of eighty patients aged between 18 and 80 years diagnosed clinically with XP and the same number of apparently healthy, age- and sex-matched controls were included in the study after giving informed consent. Detailed history taking, examinations, and investigations were performed for all patients. **Results:** Significantly raised triglycerides and LDL levels were seen in 56.3% and 66.3% of the cases, respectively. HDL levels were elevated in 63.8% of the cases and 95% of the controls, which was statistically significant. The mean levels of total cholesterol, triglyceride, LDL, and HDL were 169.68 ± 39.91 mg/dL, 159.68 ± 28.61 mg/dL, 121.23 ± 30.13 mg/dL, and 43.09 ± 8.76 mg/dL, respectively. Elevated CCAIMT and ICAIMT were seen in 87.4% and 72.8% of the cases, respectively, which was significant. **Conclusions:** There was a significant elevation of triglyceride and LDL and a decrease in HDL among the patients with XP when compared to the controls, thus making lipid profile testing compulsory for all patients with xanthelasma. They also have an increased risk of subclinical atherosclerosis, as assessed by the significantly higher values of CCAIMT and ICAIMT. Hence, all xanthelasma patients should undergo CIMT as a screening procedure for the early detection and primary prevention of cardiovascular complications.

Key words: Xanthoma; Xanthelasma palpebrarum; Dyslipidemia; CIMT; Cardiovascular morbidity

INTRODUCTION

Xanthelasma palpebrarum (XP) is the most common cutaneous xanthoma, commonly seen in middle-aged individuals [1]. It is characterized clinically by sharply demarcated, yellowish, flat plaques bilaterally on the upper and lower eyelids, usually near the inner canthus.

The exact cause is unknown, yet several factors, such as lipid abnormalities, hormonal factors, local factors, and macrophages, are attributed to play a role in its etiopathogenesis [2,3]. It may occur as a result of disturbed lipid metabolism or essential familial hypercholesterolemia, in which LDL levels are raised due to a defect in the LDL receptors, resulting in a defective uptake and degradation leading to skin lesions [1,2].

Patients with XP may have lipid abnormalities, ranging from 9.1% to 67.9% [2]. A high prevalence of atherosclerotic, vascular, and heart diseases have been reported in patients with XP with both elevated and normal lipid levels [2,4]. Meanwhile, according to other authors, it seems to have no significant relation with lipid metabolism [5].

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Carotid intima–media thickness (CIMT) is a non-invasive method of monitoring subclinical atherosclerotic plaque formation and its progression. An increased intima–media thickness (IMT) correlates with an increased risk of cardiovascular events, such as myocardial infarction and stroke. An increase in IMT of 0.1 mm has been reported to increase the relative risk of coronary disease by 11%. It is considered a surrogate marker of more generalized atherosclerosis and a risk factor for cardiovascular disease [6,7].

Although XP is a benign lesion producing no functional defects, we have to be aware of the possible cardiovascular and metabolic comorbidities that may be associated with it.

In our study, in addition to assessing the lipid profile pattern associated with XP, we also included a measurement of CIMT. Only several studies have been conducted on CIMT in patients with XP. Hence, this study was conducted to assess the association of XP with atherosclerosis and other cardiovascular abnormalities by measuring the CIMT and serum lipid profile. This association, if significantly present, may prove to be an aid in the early intervention and proper management of patients to prevent unwanted cardiovascular complications.

MATERIALS AND METHODS

This was a case–control, observational study conducted over a period of two years at the outpatient department (OPD) of Dermatology, Venereology, and Leprology in collaboration with the Department of Radiodiagnosis of the Regional Institute of Medical Sciences (RIMS) in Imphal, India. A total of eighty patients aged between 18 and 80 years clinically diagnosed to have XP and the same number of healthy, age- and sex-matched controls were included in the study after giving informed consent. Patient confidentiality was maintained throughout the study.

The exclusion criteria were:

- Study subjects on drugs known to interfere with the lipid levels in the blood;
- Pregnant and lactating mothers;
- Study subjects with comorbid conditions, such as hypothyroidism, hyperthyroidism, and nephrotic syndrome, and females on oral contraceptive pills.

Consecutive sampling was performed. Both cases and controls were subjected to proper history taking, clinical examinations, laboratory tests, and CIMT measurements.

The serum lipid profile was measured after a fasting period of eight hours at minimum. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were measured with the enzymatic endpoint method.

Dyslipidemia was diagnosed based on the NCEP ATP III guidelines:

- TC: > 200 mg %;
- HDL: < 40 mg %;
- TG: > 150 mg %;
- LDL: > 100 mg %.

CIMT was measured with B-mode ultrasonography for carotid IMT measurement (Samsung Medison SonoAce X8; Seoul, South Korea). Intima–media thickness was measured as a distance between the leading edge of the first echogenic line of the wall of the carotid artery (lumen–intima interface) and the leading edge of the second echogenic line (media–adventitia interface) during the end of the diastole (peak of the R wave on electrocardiogram) at two segments: at the point of proximal 1 cm and distal 1 cm from the common carotid artery bifurcation (Figs. 1a and 1b). Measurements were taken only on longitudinal scans and not on transverse scans. The cutoff for the upper limit of the normal for carotid intima–medial thickness was 0.8 mm [7].

Data analysis was performed with SPSS, version 21.0. For inferential statistics, the chi-squared and Fisher exact tests were employed and a p value of < 0.05 was considered statistically significant. Student's t-test were employed for comparing between means. The strength of association was presented by odds ratios at a 95% confidence interval.

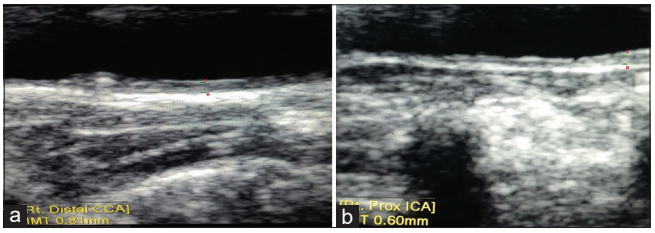

Figure 1:(a) Longitudinal scan of the common carotid artery on B-mode ultrasound. The measurement was taken as the distance between point A—the leading edge of the first echogenic line of the wall of the carotid artery (lumen–intima interface)—and point B—the leading edge of the second echogenic line (media–adventitia interface). (b) Longitudinal scan of the internal carotid artery on B-mode ultrasound. The measurement was taken as the distance between point A—taken at the lumen–intima interface—and point B—taken at the media–adventitia interface.

Ethics Statement

Ethical approval was obtained from the ethics committee of the institute.

RESULTS

A majority of the cases and controls were in the age group of 41–50 years (43.8%; $n = 35$), followed by 51–60 years (26.3%; $n = 21$), and 31–40 years (21.3%; $n = 17$). The age range was 33–64 years.

A majority were females (60%; $n = 48$), while the rest (32%; $n = 32$) were males.

A majority of the patients had a disease onset between 41 and 50 years with the mean age of onset of 43.90 ± 8.04 years. 88.7% of the patients had XP for more than two years (Table 1).

Hypertension was found in 40% of the cases and 26.3% of the controls, while diabetes was found in 21.3% of the cases and 28.8% of the controls. However, these findings were not statistically significant.

A history of smoking was present in 25 cases (31.3%) and 11 (13.8%) controls, which was statistically significant ($p = 0.008$). A sedentary lifestyle was present in 85% of the cases when compared to 68.8% of the controls, which was also statistically significant ($p = 0.015$). Low, moderate, and heavy alcohol intake was found in 18.8%, 11.3%, and 5% of the cases and 6.3%, 8.8%, and 3.8% of the controls, respectively. A habit of oral tobacco intake was present in 46.3% of the cases and 37.5% of the controls.

A positive family history of xanthelasma was found to be more common among the cases (22.5%) than among the controls (7.5%), which was significant ($p = 0.008$) (Table 2).

The mean BMI of the cases and controls was 25.75 ± 3.03 and 25.40 ± 2.81, respectively (Table 3).

The unilateral eyelid was affected only in 10% of the cases, with most cases (42.5%) having bilateral eyelid involvement (Table 4). All four eyelids were involved in 33.7% of the cases (Fig. 2).

The most common morphological type of xanthelasma was the plaque type (85%; $n = 68$), followed by the papule type (15%; $n = 12$).

Elevated cholesterol was found in 15.1% of the cases ($n = 12$) when compared to 12.5% ($n = 10$) of the controls. The mean levels of serum cholesterol among the cases and controls were 169.68 ± 39.91 mg/dL and 169.09 ± 36.32 mg/dL, respectively, which was not significant.

Triglyceride levels were elevated in 56.3% of the cases ($n = 35$) and 13.8% ($n = 11$) of the controls, and the distribution was found to be statistically significant ($p < 0.001$). The mean triglyceride levels among the cases and controls were 159.68 ± 28.61 mg/dL and 141.14 ± 13.96 mg/dL, respectively.

LDL levels > 100 mg/dL were found in 66.3% of the cases ($n = 53$) and 42.4% of the controls ($n = 34$), which was statistically significant ($p = 0.009$). The mean LDL levels in the cases and controls were

Table 1: Duration of XP in months in the study population

Duration of XP (months)	No. of patients	Percentage (%)
< 24	9	11.3%
24–47	31	38.7%
48–72	28	35.0%
➢ 72	12	15.0%
Total	80	100.0%

Table 2: Distributions of family histories in the two groups of the study population

Family History	Cases ($n = 80$)	Controls ($n = 80$)	*p* value
Xanthelasma palpebrarum	18 (22.5%)	6 (7.5%)	0.008**
Diabetes	22 (27.5%)	17 (21.3%)	0.357
Hypertension	32 (40%)	41 (51.3%)	0.153
Dyslipidemia	17 (21.3%)	10 (12.5%)	0.140
Obesity	20 (25%)	12 (15%)	0.114
Ischemic heart disease	11 (13.8%)	9 (11.3%)	0.633
Cerebrovascular accident	14 (17.5%)	7 (8.8%)	0.101

Table 3: BMI (kg/m^2) distribution in the two groups of the patients studied

BMI (kg/m^2)	Cases	Controls
< 18.5	0 (0%)	1 (1.2%)
18.5–24.9	33 (41.2%)	32 (40%)
25–30	43 (53.8%)	47 (58.8%)
➢ 30	4 (5%)	0 (0%)
Total	80 (100%)	80 (100%)

Table 4: Pattern distribution in the two groups of the patients studied

Pattern	Cases	Percentage
Unilateral	8	10%
Bilateral	34	42.5%
Three eyelids	11	13.8%
Four eyelids	27	33.7%
Total	80	100%

121.23 ± 30.13 mg/dL and 105.59 ± 25.13 mg/dL, respectively.

HDL levels were elevated in 63.8% ($n = 51$) of the cases and 95% ($n = 76$) of the controls, which was statistically significant ($p = 0.001$). The mean levels of HDL in the cases and controls were 43.09 ± 8.76 mg/dL and 50.41 ± 7.87 mg/dL, respectively.

A majority of the cases (87.4%; $n = 70$) had an elevated CCAIMT when compared to controls (4.9%; $n = 4$), which was significant ($p < 0.001$). A majority of the cases (72.8%; $n = 59$) also had an elevated ICAIMT when compared to the controls (1.2%; $n = 1$), which was significant ($p < 0.001$).s

Table 5 shows the mean values of CCAIMT and ICAIMT in the cases and controls, which were statistically significant ($p < 0.001$).

DISCUSSION

Females outnumbered males in our study, with a male-to-female ratio of 2:3, similarly to studies by Sharma et al. [1] and Kampar et al. [3]. This may have been due to the fact that females are cosmetically more conscious. A majority of the patients belonged to the age group of 41–50 years (43.8%), followed by 51–60 years (26.3%), similarly to findings by Nair et al. [8] and Kavoussi et al. [9]. In our study, a majority of the patients (38.8%) had xanthelasma for 24–48 months,

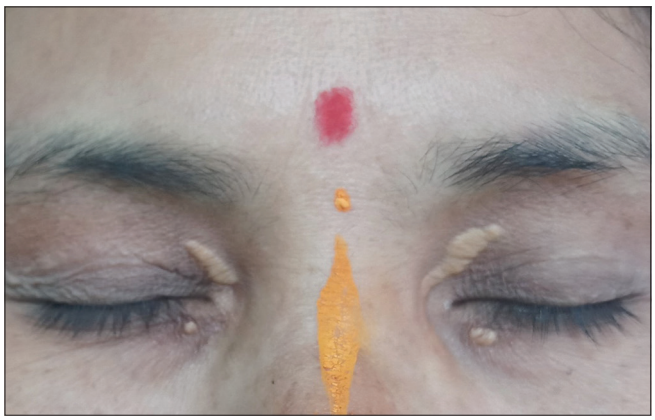

Figure 2: Well-defined, soft, yellowish papules and plaques around the medial canthus of the upper and lower eyelids.

Table 5: Comparison of CCAIMT and ICAIMT in the cases and the controls.

Variables	Cases	Controls	Total	*p* value
CCAIMT	0.90±0.12	0.49±0.12	0.69±0.24	< 0.001
ICAIMT	0.86±0.15	0.48±0.11	0.67±0.23	< 0.001

although Shankar et al. [10] found the duration of less than one year to be more common.

Hypertension was found to be more common among the cases, whereas diabetes mellitus was found to be more common among the controls, although it was not a significant finding. A history of smoking and a sedentary lifestyle was more commonly observed among those with xanthelasma, which was also significant statistically. However, no association could be found between alcohol intake and xanthelasma. Oral tobacco use was present in 46.3% of the cases, which was much higher than that reported by Dey et al. (13.1%) [11].

A family history of xanthelasma palpebrarum was found in 22.5% of the cases when compared to 7.5% of the controls, which was statistically significant ($p = 0.008$), implying that there is a higher proportion of a positive family history of xanthelasma among the cases than the controls.

There was no significant difference between the mean BMI of the cases and the controls.

A majority of the patients had plaque morphology (85%), followed by papule morphology of XP (15%). Bilateral eyelids involvement was found in a majority of the cases (42.5%), similarly to the findings by Dey et al. [11].

In our study, 15.1% ($n = 12$) of the cases and 12.5% ($n = 10$) of the controls had elevated serum cholesterol levels. The mean levels of serum cholesterol were almost equal in the cases and controls. The cases having total cholesterol ≤ 200 mg/dL were 19% less likely to develop xanthelasma when compared to the controls.

Significantly elevated triglyceride levels were seen in 56.3% of the cases ($n = 45$) and 13.8% ($n = 11$) of the controls. The cases with triglycerides ≤ 150 mg/dL were 88% less likely to develop xanthelasma when compared to the controls. The mean triglyceride level among the cases was found to be higher than among the controls, which was consistent with findings by Aggarwal et al. [12].

LDL levels were elevated in 66.3% of the cases ($n = 53$) and 42.4% of the controls ($n = 34$). The cases having LDL ≤ 100 mg/dL were 63% less likely to develop xanthelasma when compared to the controls, and the mean LDL level was higher among the cases than the controls. This finding was similar to a study by Shankar

et al. [10], who reported statistically significant elevated LDL in 82% of the cases. This was higher than the findings by Platsidaki et al. [13].

HDL level was found to be elevated in 63.8% ($n = 51$) of the cases and 95% ($n = 76$) of the controls with higher mean levels in the controls than the cases, which was significant statistically. The cases with low HDL were ten times more likely to develop xanthelasma when compared to the controls. This observation was in contrast with that by Sharma et al. [1], who reported no difference in HDL between the cases and the controls.

A majority of the cases (87.7%; $n = 70$) had an elevated CCAIMT when compared to the controls (4.9%; $n = 4$). Similarly, a majority of the cases (72.8%; $n = 59$) had an elevated ICAIMT when compared to the controls (1.2%; $n = 1$), which was also statistically significant ($p < 0.001$). The cases with CCAIMT and ICAIMT ≤ 0.8 mm were 99% less likely to have xanthelasma when compared to the controls. The mean values of CCAIMT and ICAIMT were significantly higher ($p < 0.001$) in patients with xanthelasma. This result was in agreement with that by Pandhi et al. [14], who reported significantly higher mean values of CCAIMT and ICAIMT in patients with xanthelasma in addition to more elevated ICAIMT and CCAIMT in the cases than the controls. Esmat et al. [15] reported a higher IMT in patients with XP, especially in those with hyperlipidemia. However, Chan et al. [5] reported that the presence of XP was not associated with an increase in CCAIMT.

CONCLUSION

There were significant abnormalities in LDL, HDL, and triglyceride levels in the patients with XP when compared to the controls. Hypertension and diabetes mellitus were the commonly associated comorbid diseases. Our result also indicated that patients with xanthelasma also had an increased risk of subclinical atherosclerosis as assessed by the significantly higher values of CCAIMT and ICAIMT. Hence, it is advisable for patients with XP to undergo lipid profile testing and CIMT measurements as a screening procedure for the early detection and primary prevention of CAD.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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