Relationship between plasma atherogenic index and xanthelasma palpebrarum

Sri Karunia Setio Wati*, Imam Budi Putra*, Nelva Karmila Jusuf

ABSTRACT

Introduction: Xanthelasma is a common form of skin xanthoma. It is due to abnormal lipid deposition in the eyelid skin. Xanthelasma is thought to be a sign of dyslipidemia, one of the important risk factors in atherosclerosis. The risk of atherosclerotic disease can be determined using the atherogenic index of plasma (AIP) parameters. AIP is a mathematical relationship between TG and HDL in logs (TG/HDL). Thus, this study aimed to determine the relationship between the atherogenic index of plasma and xanthelasma palpebrarum at the Polyclinic of the Department of Dermatology and Venereology, Universitas Sumatera Utara Hospital.

Methods: This study was an observational analytic study with a cross-sectional approach involving 50 patients with xanthelasma palpebral and 50 controls based on inclusion and exclusion criteria. Gender, age, lipid profile values (cholesterol, HDL, LDL, and triglycerides), and Atherogenic Index of Plasma (AIP) values were recorded. Laboratory tests measured assessment atherogenic index of plasma to determine triglyceride (TG) and high-density lipid (HDL) levels using the Cobas 6000 CS01 device. An independent t-test was conducted to assess the relationship between research variables, and it was declared significant with p < 0.001.

Results: The majority of xanthelasma palpebrarum occurred in women (94%), and the mean value of the subjects of this disease was higher in the 50-59 year age group (42%). The mean value of lipid profile (total cholesterol, LDL, HDL, and triglycerides) in xanthelasma palpebrarum subjects tends to increase compared to subjects without xanthelasma palpebrarum. The results obtained using the logistic regression test showed that there was a significant relationship between plasma atherogenic index (AIP) values and xanthelasma palpebrarum (p < 0.001). In the group with xanthelasma palpebrarum, the highest proportion were subjects with an IAP value > 0.21 (high risk), and the risk of experiencing xanthelasma palpebrarum was 7.714 times greater than subjects with an AIP < 0.11 (low risk).

Conclusion: There is a relationship between plasma atherogenic index and xanthelasma palpebrarum.

Keywords: xanthelasma palpebrarum, atherogenic index of plasma, triglycerides, HDL, atherosclerosis


INTRODUCTION

Xanthelasma is a common form of skin xanthoma, characterized by yellowish plaques, and generally occurs on the upper eyelid (xanthelasma palpebrarum / XP). It is due to abnormal lipid deposition in the eyelid skin. In the world, the incidence is 0.56-1.5%, with the age of onset 15-73 years. Most cases occur in the fourth and fifth decades of life, with most cases in women. In Padang from 2013-2017, as many as ten new xanthelasma patients, with two male patients and eight female patients.

One of the causes of xanthelasma includes dyslipidemia, hormonal factors, local factors, and the involvement of macrophages (acetylated low-density lipids and macrophages with scavenger receptors). Xanthelasma is thought to be a sign of dyslipidemia, one of the important risk factors in developing atherosclerotic cardiovascular disease. Xanthelasmata can be found in soft, semisolid, or calcareous forms. Generally, xanthemata appear bilaterally and involve the entire eyelid. Progressive xanthelasmata tend to coalesce and become permanent. Xanthelasmata represent lipid areas containing macrophages, but their pathogenesis is still not fully understood. Other article showed that xanthelasma and atherogenic formation correlated with the same mechanism, namely upregulation of T cells, macrophages, and the inflammatory mediator INOS, COX, and this mechanism was also found in the early stages of atherosclerotic plaque formation.

The risk of atherosclerotic disease can be determined by using the atherogenic index of plasma (AIP) parameters obtained by looking at the triglyceride (TG) and high-density lipid (HDL) profiles. AIP is a mathematical relationship between TG and HDL in the form of logs (TG/HDL) and then the results are divided into three risk groups: (1) low risk, IAP < 0.11; (2) moderate risk, IAP > 0.12 and < 0.21; and (3) high risk, IAP > 0.21. Xanthelasma is a marker of dyslipidemia, a major factor causing cardiovascular disease and is often assessed from the lipid profile level. This is in line with the research finding that hyperlipidemia significantly increased in XP patients in as many as 64 cases and controls in 40 cases where (p = 0.001) and triglyceride values.
also found hyperlipidemia with high triglyceride values by 45 (55.6%) and low HDL values in both xanthelasma patients and controls. 

The results of the categorization of an atherogenic index of plasma values for xanthelasma palpebrarum subjects and control group are shown in Table 3.

### RESULTS

In this study, the dominant female sex characteristics in xanthelasma palpebrarum subjects were 47 people (94%), and subjects aged 50-59 years dominated the xanthelasma palpebrarum group as many as 21 people (42%). Characteristics by sex and age are described in Table 1.

**Table 1. Baseline characteristics of study subjects.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(n=50)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Woman</td>
<td>47</td>
<td>94</td>
</tr>
<tr>
<td>Age (years old)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 – 29</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>30 – 39</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>40 – 49</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>50 – 59</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>&gt;60</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

**Table 2. Lipid profile values in the subject group the xanthelasma palpebrarum.**

<table>
<thead>
<tr>
<th>Lipid Profile</th>
<th>Mean (SD), mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>220.63 (35.51)</td>
</tr>
<tr>
<td>HDL</td>
<td>49.41 (9.71)</td>
</tr>
<tr>
<td>LDL</td>
<td>168.28 (50.24)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>204.25 (90.12)</td>
</tr>
</tbody>
</table>

**Table 3. Relationship of an atherogenic index of plasma values for xanthelasma palpebrarum subject group and control group.**

<table>
<thead>
<tr>
<th></th>
<th>Xanthelasma palpebrarum (n=50)</th>
<th>Control (n=50)</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>27 (54)</td>
<td>7 (14)</td>
<td>&lt;0.001*</td>
<td>7,714</td>
<td>(2,822-21,087)</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>5 (10)</td>
<td>7 (14)</td>
<td>&lt;0.001*</td>
<td>1.429</td>
<td>(0.397-5.136)</td>
</tr>
<tr>
<td>Low Risk</td>
<td>18 (36)</td>
<td>36 (72)</td>
<td>0.585</td>
<td>1.532</td>
<td>(0.829-2.820)</td>
</tr>
</tbody>
</table>

*Significant value
The histogram graph of differences in the proportion of atherogenic index of plasma values between the xanthelasma palpebrarum subject and the control groups.

Subjects aged 50-59 years were dominant in the xanthelasma palpebrarum group as many as 21 people (42%). It is in line with the research conducted by Gondane. The results showed that the age group with the highest prevalence of xanthelasma palpebrarum was the 40-50 year age group (33%). The study did not find a significant difference between the two groups based on age with a p-value = 0.6299. The peak incidence of xanthelasma palpebrarum is at the age of 40-60 years. 

Xanthelasma formation begins with increased local extravasation of lipids through the vascular wall into the interstitial spaces of connective tissue. The accumulation of monocytes and macrophages is taken up by lipid particles (specific receptors) to phagocytize LDL and lipid aggregation complexes with antibodies; then foam cells are formed. Lipoproteins do not induce cell formation directly. Intracellular LDL catabolism by LDL receptors is slow, and cholesterol homeostasis is effectively regulated. Free cholesterol is released from LDL after internalization, which inhibits its synthesis. In addition, free cholesterol inhibits the synthesis of LDL receptors, thereby reducing the endocytosis of LDL by cells. 

Based on LDL levels, the mean LDL value in the group of subjects with xanthelasma palpebrarum was 168.28 mg/dL. Research conducted by Gondane found an increase in LDL values in 52 cases (71.2%) with a mean value of 137.3 mg/dL. Research conducted by Sankar also obtained similar results with LDL values in the xanthelasma palpebrarum group of 135.2 mg/dL. Research conducted by Sankar also found a significantly increased LDL cholesterol value in 82% of cases.

According to the HDL levels, the mean HDL value in subjects with xanthelasma palpebrarum was 49.41 mg/dL. Research conducted by Chaudhary found that the mean HDL value in the case group was 41.7 mg/dL. In Gondane’s study, HDL levels decreased in 34 cases (46.6%) with a mean HDL value of 41.33 mg/dL. The results of Kavoussi et al’s study also found something similar with the HDL value in the case group of 36.2 mg/dL. Low HDL cholesterol levels are also another factor that plays a role in the pathogenesis of xanthelasma palpebrarum. It is because HDL can get rid of excess cholesterol in the tissues and low levels indicate a malfunction.

Cholesterol levels also change. The mean value of total cholesterol in the group of subjects with xanthelasma palpebrarum with an average of 220.63 mg/dL, Gondane et al. report an enhancement of total cholesterol in most cases (46 cases or 63.01%), with the average total cholesterol value being 212.6 mg/dL. Several research also found similar findings, such as research conducted by Chaudhary with the mean cholesterol value in the case group of 218.5 mg/dL. The same thing was also found in a study conducted by Kavoussi et al., which found the total cholesterol value in patients was 221.51 mg/dL. Research conducted by Sankar in 2015 also found a significant increase in total cholesterol in xanthelasma palpebrarum patients with p = 0.009. Thus, we can conclude that xanthelasma palpebrarum could be a sign of enhancement of cholesterol level.

In addition, another lipid that changed besides HDL, LDL, and cholesterol was triglyceride levels; the mean value of the group of subjects with xanthelasma palpebrarum was seen with an average of 204.25 mg/dL. It is in line with Gondane’s study with an increase in triglyceride values in 29 cases (39.7%) with an average triglyceride value of 152.29 mg/dL. Research conducted by Chaudhary found triglyceride values of 171.4 mg/dL in the group of xanthelasma palpebrarum.
cases.21 Research by Kavoussi et al. found the mean triglyceride value of 185.98 mg/dL.6

The OR value obtained was 7.714 (95% CI 2.822 – 21.087), which means that subjects who have an IAP > 0.21 (high risk) are at risk of experiencing xanthelasma palpebrarum by 7.714 times greater than subjects who have an AIP < 0.11 (low risk). Subjects with IAP between 0.11 – 0.21 were not significantly associated with palpebral xanthelasma when compared with subjects with AIP < 0.11 (p = 0.585). A study conducted by Dey stated that patients with xanthelasma palpebrarum had a significantly higher thickness of the carotid intima-media because there was a significant increase in atherogenic apolipoproteins in xanthelasma palpebrarum patients, as well as an increase in mean serum cholesterol, LDL cholesterol, and triglycerides. The researchers concluded that patients with xanthelasma palpebrarum with any lesion size and serum lipid value should be screened for carotid intima-media thickness screening for early detection of subclinical atherosclerosis.9 The limitation of this study was only conducted in one center, did not assess a grading of xanthelasma, other factors that contribute to xanthelasma formation.

CONCLUSION
There is a relationship between the atherogenic index of plasma and xanthelasma palpebrarum. Based on an atherogenic index of plasma values in the group of subjects with xanthelasma palpebrarum, the highest proportion were subjects with an atherogenic index of plasma values > 0.21 (high risk) and 7.714 times greater risk of experiencing xanthelasma palpebrarum than subjects with AIP < 0.11 (risk of low).

DISCLOSURE
Author Contribution
All authors have contributed to this research process, including preparation, data gathering, analysis, drafting, and approval to publish this manuscript.

Funding
The authors are responsible for all of the study funding without a grant or any external funding source.

Conflict of Interest
The authors declare no conflict of interest regarding the publication of this article.

Ethical Consideration
This research has obtained ethical clearance from the Research Ethics Commission of the Faculty of Medicine, Universitas Sumatera Utara, and a Research Permit from the Hospital of the Universitas Sumatera Utara.

ACKNOWLEDGMENTS
We want to express gratitude to the Head of the Department of Dermatology and Venereology of the Faculty of Medicine, Universitas Sumatera Utara and University of North Sumatra Hospital.

REFERENCES
19. Gondane S, Ashok M, Rajkumar K. To Study the Prevalence of Metabolic
Syndrome and Dyslipidemia in Patients of Xanthelasma Palpebrarum at a Tertiary Care Hospital. Indian J Clin Pract. 2020;31(4).


