

# The Correlation Between Lipid Profile and Xanthelasma

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## ABSTRACT

**Background:** Xanthelasma is an abnormal lipid deposition on palpebrae, which is observable as yellowish plaque or nodules. Its incidence is 0.56–1.5% with onset of 15–73 years old and mostly occurs in the fourth and fifth decade. Few reports of xanthelasma did not cover the correlation between lipid profile and xanthelasma in Indonesia. **Purpose:** To find a correlation between lipid profile with xanthelasma in Dr. M. Djamil Hospital, Padang. **Methods:** This was an analytic cross-sectional study with consecutive sampling. There were 36 participants (18 xanthelasma and 18 control). **Result:** The highest age group was >36 - ≤45 years old (38.89%). More cases were observed in female (66.67%). Body mass index examination of xanthelasma revealed that most were overweight (55.56%). Grade I xanthelasma was the most common (72.22%). The cholesterol serum level of xanthelasma patients was higher than the subject controls (224.61±29.77 mg/dl versus 169.39±35.84 mg/dl) ( $p<0,05$ ). The High Density Lipoprotein (HDL) serum level of xanthelasma patients was lower than controls (46.44±14.19 mg/dl versus 51.78±15.9 mg/dl) ( $p>0,05$ ). The Low Density Lipoprotein (LDL) serum level of xanthelasma patients was higher than control (139.39±29.73 mg/dl versus 106.50±35.43 mg/dl) ( $p<0,05$ ). Triglyceride serum level of xanthelasma patients was higher than the controls (167.83±87.26 mg/dl versus 121.61±54.52 mg/dl) ( $p>0,05$ ). **Conclusion:** There was a correlation between higher cholesterol and LDL serum level with xanthelasma. No correlation between lower HDL and a higher triglyceride serum level with xanthelasma.

**Keywords:** xanthelasma, lipid profile.

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## BACKGROUND

Xanthelasma is the most common form of cutaneous xanthoma, an abnormal lipid deposition on the eyelids, and it presents as a yellowish plaque or nodule.<sup>1-3</sup> Xanthelasma might feel tender, soft, semisolid, or calcareous upon palpation. Xanthelasma is usually symmetrical, might occur on the whole eyelid and might expand permanently.<sup>1,2,4,5</sup>

The incidence of xanthelasma varies around 0.56–1.5% worldwide, the age of onset is 15–73 years old, and most cases occur in the fourth and fifth decade of life.<sup>2,3,6-8</sup> A study by Laftah in London (2018) stated that the prevalence of xanthelasma was 4%, with a 0.3% incidence in men and 1.1% in women.<sup>9</sup> The incidence of xanthelasma in Copenhagen (2011) was 4.4% and 0.09% in South Korea in 2017.<sup>10,11</sup> Xanthelasma is more common in women than men, and its incidence increases with age.<sup>1,6,7,12-14</sup> There were 91 patients with xanthelasma in the outpatient clinic of the Dermatovenereology Department, Faculty of Medicine of Universitas Indonesia/Cipto Mangunkusumo Hospital from 2007 to 2009.<sup>2</sup> The xanthelasma incidence in the outpatient clinic of Mataram Hospital was 18.2%.<sup>15</sup> In the outpatient clinic of Dermatovenereology Department of Dr. M. Djamil

Central Public Hospital Padang, there were 16 new xanthelasma patients between 2013 and 2017.<sup>16</sup>

Patients usually present with complaints of a cosmetic disorder, which often makes them less confident; therefore, affecting their quality of life. However, to our knowledge, there has been no xanthelasma study which uses the Dermatology Life Quality Index (DLQI). Those studies usually only mention how xanthelasma alters the patient's quality of life cosmetically to the point that it interferes with their daily activity. Therefore, early detection is needed to prevent cosmetic disorder, lack of confidence, and less quality of life. These studies did not present quantitative data on how much xanthelasma affects the cosmetic aspect, sense of confidence, and quality of life.<sup>1,5,17-20</sup>

Xanthelasma has been considered as a marker for atherosclerosis, which is the main factor of cardiovascular diseases. Recently, the incidence of metabolic diseases tends to increase due to lifestyles, dietary habit, and metabolic disorder, which also increases the incidence of xanthelasma.<sup>1,5,17-20</sup> Dwivedi et al., conducted a study on xanthelasma as a marker for atherosclerosis in India. The study concluded that there was a tendency of coronary arterial disease and

asymptomatic atherosclerosis in familial xanthelasma.<sup>21</sup> Dey reported xanthelasma cases in individuals with other predisposing factors such as smoking, central obesity, hypertension, diabetes mellitus, and dyslipidemia in India. These are the main risk factors for congestive arterial disease. Furthermore, Zac in the Czech Republic (2014) reported that xanthelasma correlates to an increased risk for atherothrombotic disease.<sup>3,4,21,22</sup> It is presumed that xanthelasma can act as a marker for dyslipidemia and also it might predict the possibility of someone acquiring coronary artery disease due to dyslipidemia. Therefore the occurrence of xanthelasma in an individual should make health workers aware of dyslipidemia and atherosclerosis.<sup>4,23</sup>

The main pathogenesis of xanthelasma is unclear, although several factors might take part, such as dyslipidemia, hormonal factors, local factors, and macrophages, acetylated Low Density Lipoprotein (LDL) and macrophages with scavenger receptor.<sup>24</sup> In Italy, Caputo R reported one xanthelasma case in a normolipidemic patient.<sup>25</sup> There were also reports from Bergman R in the United States and Sharma SB in India that stated 20-70% xanthelasma in normolipidemic patients.<sup>7,8</sup> In contrary to the studies mentioned above, a study by Christoffersen in Copenhagen (2011) reported the ratio of myocardial infarct was 1.48 in xanthelasma patients compared to control group (mean 1.231.79; confidence interval 95%), 1.39 (1.201.60) for ischemic heart disease, 0.94 (0.731.21) for ischemic stroke, and 0.91 (0.721.15) for ischemic cerebrovascular disease, and 1.14 (1.041.26) for the mortality rate.<sup>26</sup>

About 50% of xanthelasma cases were reported with hyperlipidemia (increased serum cholesterol). Xanthelasma with hyperlipidemia correlates to its underlying primary or secondary disease, while in normolipidemic patients, other contributing factors are hormonal and genetic factors. Xanthelasma in young adults with familial history of hyperlipidemia should be suspected of the presence of lipid metabolism disorder.<sup>1,7,17,24</sup> The lipid profile is a summary of the blood lipid level. A number of properties checked in lipid profiles are cholesterol, High Density Lipoprotein (HDL), LDL, and triglycerides. The normal level of cholesterol is <200 mg/dl, HDL >40 mg/dl, LDL <100 mg/dl, and triglycerides <150 mg/dl.<sup>27-29</sup>

A study by Ozdol in Turkey (2008) compared 100 xanthelasma patients with a control group, and the study concluded that xanthelasma patients also had dyslipidemia.<sup>20</sup> A study by Noel in Swiss (2007) reported that, out of 17 xanthelasma patients aged 31–73 years old and 21 control patients aged 23–75 years old, there were 7 people with normolipidemic

xanthelasma and 8 hyperlipidemic people without xanthelasma.<sup>30</sup> Furthermore, a study by Dey in India (2013) reported that out of 61 xanthelasma patients, there were 12 dyslipidemic patients, and 49 normolipidemic patients, while out of 130 individuals in the control group, there were 28 dyslipidemic and 102 normolipidemic individuals.<sup>4</sup> Szalat et al. in Italy (2011) reported that 2 out of 24 patients were hyperlipidemic.<sup>31</sup> Bergman in Israel in 1994 reported normal cholesterol and triglycerides level in xanthelasma patients.<sup>32</sup> To the knowledge of the authors, there has been no study evaluating the correlation between lipid profile and xanthelasma in Indonesia. Therefore, we were motivated to investigate the topic.

## METHODS

This was a cross-sectional, observational analytic study. The study aimed to evaluate the correlation between lipid profile and xanthelasma. The inclusion criterion was xanthelasma patients (new and old cases) aged >18 years old who are willing to participate in the study by signing informed consent. The exclusion criterion was patients whose under lipid treatment within the last one month. We used a consecutive sampling method, choosing the subjects based on attendance at the Dermatovenereology outpatient clinic of Dr. M. Djamil Hospital, Padang. This study has approved an ethical clearance from Dr. M. Djamil Hospital, Padang.

## RESULT

The group with the highest prevalence of xanthelasma was the >41 – ≤50 years old (38.89%). There were more women with xanthelasma than men (66.67%). The mean age of the xanthelasma group was 48.61±12.36 years old, and the mean onset was on 48.11±12.27 years old. The body mass index on the xanthelasma group was 25.33±1.13. Grade I of xanthelasma was the most commonly found, which was 72.22%. More than two-thirds of the study sample had the age onset of > 40 years old (61.11%) (Table 1).

The xanthelasma group had a higher total cholesterol level, which was 224.61±29.77 mg/dl, than the control group, which was 169.39 ± 35.84 mg/dl (p<0,05). This group had a lower HDL level, which was 46.44±14.19 mg/dl, than the control group, which was 51.78±15.94 mg/dl (p>0,05). The LDL level that was 106.50±35.43 mg/dl was higher than that of the control group, which was 106.50±35.43 mg/dl. The summary of the triglycerides level of the xanthelasma and control group can be seen in Table 2. The triglycerides level in the xanthelasma group, 167.83±87.26 mg/dl, was higher than that of the

control group, which was  $121.61 \pm 54.52$  mg/dl ( $p > 0.05$ ).

There was a tendency of a positive correlation of the cholesterol levels on xanthelasma patients compared to the control group. The correlation test

result showed that the cholesterol and LDL level between xanthelasma and controls was statistically significant if  $p < 0.05$ . The cholesterol and HDL level between xanthelasma and controls were statistically not significant if  $p > 0.05$ .

**Table 1.** The distribution of xanthelasma patients and control subjects in Dr. M. Djamil Hospital Padang, January – December 2018

Characteristics	Xanthelasma		Control		p
	f (n = 18)	(%)	f (n = 18)	(%)	
<b>Age</b>					
> 18 - ≤ 30 years	-	-	-	-	
> 31 - ≤ 40 years	6	33.33	6	33.33	
> 41 - ≤ 50 years	7	38.89	7	38.89	
> 51 - ≤ 60 years	2	11.11	1	5.56	
> 61 years	3	16.67	4	22.22	
Mean ± standard deviation	48.611±12.358		48.111±12.266		0.8
<b>Sex</b>					
Male	6	33.33	6	33.33	-
Female	12	66.67	12	66.67	
<b>Body Mass Index (BMI)</b>					
Underweight (< 18,4)	-	-	-	-	0.7
Normal weight (18,5-24,9)	6	33.33	16	88.89	
Overweight (25-29,9)	10	55.56	2	11.11	
Obese (30-39,9)	2	11.11	-	-	
<b>Xanthelasma classification</b>					
Grade I	13	72.22	-	-	
Grade II	3	16.67	-	-	
Grade III	1	5.56	-	-	
Grade IV	1	5.56	-	-	
<b>Age of onset for xanthelasma</b>					
≤ 40 years	7	38.89	-	-	
> 40 years	11	61.11	-	-	
Mean ± standard deviation age of onset	43.389±10.122				

Note : frequency = 36 P = p value (CI = 95%)

**Table 2.** Serum lipid profile

Lipid profile	Xanthelasma	Control	p
Total cholesterol (mg/dl)	224.61±29.77	169.39±35.84	0.000*
HDL (mg/dl)	46.44±14.19	51.78±15.94	0.297
LDL (mg/dl)	139.40±29.73	106.50±35.43	0.005*
Triglycerides	167.83±87.26	121.61±54.52	0.065

Note : SD = ±2 ; P=0,001 Cholesterol = 29.77; High Density Lipoprotein =14.19; Low Density Lipoprotein = 29.73; Triglyceride = 87.26

## DISCUSSION

The results showed that most patients with xanthelasma were in the >41 - ≤50 years age group. This is in line with a study by Dey in India (2013) and Reddy et al., in England (2013) which showed that the highest incidence of xanthelasma cases was in the 31-40 and 40-50 years age group. Gangopadadhy et al., (2007) also acquired the highest incidence of xanthelasma cases (30%) in the 31-40 years age group. A similar result was obtained by Jain in India (2007), in which the majority of xanthelasma patients were 31-50 years old (37.9%).<sup>24</sup> Chhetri in India in 2008 found that the highest incidence of xanthelasma was from the 40-50 years age group and 40% of the cases were from the 30-40 years age group.<sup>17,24</sup>

Dey in India (2013) found that of 34 males and 27 females xanthelasma patients, 6 patients were ≤ 40 years old, 45 patients were 40 - 60 years old (73.77%), and 10 patients were ≥ 60 years old. The author classified the site of the lesion(s) into unilateral (15 patients), bilateral (30 patients), affecting 3 eyelids (6 patients), and 4 eyelids (10 patients).<sup>4,18,32</sup>

The correlation test of this study was  $p=0.8$  ( $p>0.05$ ). Thus, it was inferred that there was no significant difference between the patients' age and the control subjects. Therefore, the age characteristic bias can be minimized.

The epidemiology data from a number of studies show that xanthelasma is more commonly found in females.<sup>2</sup> In this study, there were 12 females (66.67%) and 6 males (33.33%), with a ratio of 2:1. A study by Anggarwal in India (2016) reported that 80.95% of xanthelasma cases were females. Similar results were reported by Jain in India (2007) and Gangopadhy, Epstein, and Pedace in Brazil in 2016.<sup>17,24</sup> Kavoussi in Iran (2015) acquired similar result; xanthelasma is more common in females (85.7%) than males (14.3%); however, this contradicts to a study by Dey in India (2013) who reported that there were more cases in males (55.7%) than females (44.3%).<sup>4</sup> Theoretically, the predominance of xanthelasma in females is due to hormonal factor (estrogen) in the etiopathogenesis of xanthelasma and the deeper concern to cosmetics in females.<sup>18</sup>

A study by Jain in 2007 stated that the age of onset of xanthelasma is highest in the fourth and fifth decade of life. In this study, 61.11% of patients had the onset age of > 40 years and 38.89% of ≤ 40 years old. A similar result was reported in a study by Kavoussi in 2015, where 45.23% were > 40 years old and 19% > 50 years old when they first contracted xanthelasma.<sup>18</sup>

The body mass index (BMI) examination revealed that 10 patients (55.56%) were overweight, 6 patients (33.33%) were normoweight, and 2 patients

(11.11%) were obese. BMI might affect the lipid profile. A study by Akyuz AR in Turkey (2016) found that there was a positive correlation between xanthelasma and the BMI, in which the BMI of xanthelasma patients was  $31.2\pm 5.6$  (overweight).<sup>19,33</sup>

The clinical classification showed that the majority of patients, 72.22%, suffered from grade I xanthelasma. This is following a report by Kavoussi in 2015, in which 57.14% of research subjects suffered mild grades.<sup>18</sup> Jain classified xanthelasma based on palpebral involvement instead of grading. The study reported that the majority of patients, which was 91.0% suffered from multiple lesion. In 87.9% of the cases, xanthelasma affected two or more eyelids. A study by Chetri and Ribera also reported that xanthelasma affected two or more eyelids in most of the patients.<sup>24</sup>

Kavoussi in 2015 reported a mean cholesterol level of  $221.51\pm 60.4$  mg/dl in xanthelasma patients.<sup>18</sup> In this study, the total cholesterol level was  $224.61\pm 29.77$  mg/dl in affected patients, which was higher than that in control subjects,  $169.39\pm 35.83$  mg/dl. Corresponding to a study by Pandhi in India, there was a similar result. The study reported an increased cholesterol level in xanthelasma patients compared to the control group.<sup>19</sup>

Pandhi reported that 67.5% of xanthelasma patients had normal cholesterol levels.<sup>19</sup> In this study, there were two patients (22.22%) with normal cholesterol levels (<200 mg/dl). Cases of xanthelasma with normal lipid levels (normolipid) were reported by Noel in Swiss in 2007. The same study also reported the risk of premature carotid atherosclerosis in xanthelasma patients, both normolipidemic and hyperlipidemic. It is then inferred that there is an increased risk of cardiovascular disease in xanthelasma patients.<sup>30</sup> The lipid profile can be affected by one's age and sex. In this study, the age and sex between xanthelasma patients and control subjects were equalized to minimize bias. In addition, the test result was  $p>0.05$ ; therefore, the age and sex differences in this study were not statistically significant.

A study by Kavoussi in Iran in 2015 reported an HDL level of  $36.2\pm 31.41$  mg/dl and  $50.5\pm 44.5$  mg/dl in control subjects.<sup>18</sup> This study HDL level of  $46.44\pm 14.19$  mg/dl in patients and  $51.78\pm 15.94$  mg/dl in the control group, which is less than the normal level, < 40 mg/dl. Our study obtained similar results to that of Kavoussi's, in which the HDL level of xanthelasma patients was lower compared to the control group. This is in accordance with a study by Pandhi, where the HDL level of xanthelasma patients was lower.<sup>19</sup>

High-density lipoprotein is a non-atherogenic lipid component. At its low level, the atheroprotective

component in the body that protects from atherosclerosis is also decreased. In contrary, if the HDL level is high, the risk for atherosclerosis decreases; therefore, reducing the risk of coronary heart disease and stroke.<sup>34</sup>

Kavousi's study reported the mean LDL level of  $120.3 \pm 43.6$  mg/dl in affected individuals and  $110.6 \pm 26.7$  mg/dl in the control group.<sup>18</sup> This study found that the mean of LDL level of xanthelasma patients was  $139.40 \pm 29.73$  mg/dl, which was higher than the control group,  $106.50 \pm 35.43$  mg/dl. Pandhi also obtained similar results, an higher LDL level in xanthelasma patients compared to the control group.<sup>19</sup> A study by Akyus in 2016 acquired identical result; the LDL level ( $142 \pm 45$  versus  $115 \pm 36$  mg/dl,  $p = 0.003$ ) in xanthelasma compared to the controls.<sup>33</sup>

Low Density Lipoproteins serve as a carrier for cholesterol, triglycerides, and other blood fat to various parts of the body. Specifically, the main function of LDL is to transport cholesterol from the liver to tissues by mounting it to the cell membrane.<sup>35</sup> A lower LDL level is low will result in cholesterol buildup in the blood. This will facilitate acetylation and cholesterol leakage from the blood vessel, causing xanthelasma.<sup>2,6</sup>

Kavousi in 2015 reported triglyceride level of  $185.98 \pm 71.7$  mg/dl in xanthelasma patients and  $149.39 \pm 94.2$  mg/dl in the control group.<sup>18</sup> In this study, the triglyceride level of the patients' group was  $167.83 \pm 87.2611$  mg/dl, which was higher than the control group,  $121.61 \pm 54.52$  mg/dl. This is in accordance with a study by Pandhi which reported a higher triglyceride level in xanthelasma patients compared to the control group.<sup>19</sup> A study by Akyus in 2016 obtained an identical result, reporting a higher lipid profile level in xanthelasma than the control group.<sup>56</sup> Age and sex may affect the lipid profile level; however, in this study, age and sex were homogenized.

There has been a tendency to a positive correlation, a higher cholesterol level in xanthelasma patients than the control group. The test showed a statistically significant result between the cholesterol and LDL levels in which  $p < 0.05$ .

Abnormal lipid metabolism is an important factor in the pathogenesis of xanthelasma. It has been studied that LDL was found along the capillary wall of xanthelasma patients, meaning that the accumulation of cholesterol originates in the blood. Therefore, studies on the relationship between xanthelasma and hyperlipidemia have been largely done to prove whether cholesterol level and LDL were significantly higher in xanthelasma patients compared to control subjects.<sup>20</sup> A study by Jain involving 66 xanthelasma patients and 50 control subjects, there was a

statistically significant rise in cholesterol level (216.8 mg/dl in xanthelasma patients and 173.6 mg/dl in control subjects) with  $p = 0.001$  ( $p < 0.05$ ) and CI = 95%.<sup>24</sup>

Pandhi in India and Kavoussi in Iran reported a statistically significant correlation between cholesterol and xanthelasma.<sup>18,19</sup> However, Bergman (1994) in United States reported the opposite that there were normolipidemic xanthelasma patients.<sup>32</sup>

A higher serum cholesterol level is one of the many major risk factors for coronary heart disease.<sup>24</sup> Xanthelasma is widely associated with the rise in blood lipid levels, one of which is cholesterol. Therefore, xanthelasma can also serve as a marker to determine the risk factor for coronary heart disease. A focus of therapy is to reduce risk factors by decreasing the cholesterol level.<sup>24,35,36</sup>

A study by Esmat in Egypt (2015) also obtained a similar result, in which the HDL level was not statistically significant between xanthelasma patients and the control group. A study of Esmat compared normolipidemic with hyperlipidemic xanthelasma patients. The study reported that the HDL level of 20 normolipidemic xanthelasma patients was  $45.72 \pm 8.00$  mg/dl and  $45.39 \pm 7.15$  mg/dl in the control group. Additionally, the LDL level of 20 hyperlipidemic xanthelasma patients was  $29.14 \pm 3.46$  mg/dl, and the control group was  $45.39 \pm 7.15$  mg/dl.<sup>37</sup>

In Said's study, the risk factors for atherosclerosis were studied and concluded that normolipidemic xanthelasma patients have a higher risk of atherosclerosis than hyperlipidemic xanthelasma patients; therefore, monitoring and early treatment are needed.<sup>37</sup> In this study, there were 8 patients (44.44%) with an HDL level of  $< 40$  mg/dl, in which HDL is an atheroprotective lipid against blood vessel atherosclerosis risk factors. It is then suggested that patients should have early monitoring of their atherosclerosis risk factors.

Higher LDL level in xanthelasma groups compare to controls also reported by Akyus from Turkey in 2016, Kavousi from Iran in 2015, and Pandhi from India in 2012.<sup>18,19,33</sup> It is contrary to the results from Esmat's study (2015), where the LDL levels were not statistically significant in the xanthelasma and control group. The study recorded that LDL level in normolipidemic xanthelasma patients was  $106,25 \pm 18,69$  mg/dl and controls was  $99,79 \pm 26,24$  mg/dl; in hyperlipidemic xanthelasma patients  $134 \pm 26,51$  mg/dl and controls was  $106,25 \pm 18,69$  mg/dl.<sup>37</sup>

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function of LDL is to transport cholesterol from the liver to tissues by mounting it to the cell membrane.<sup>35</sup> A lower LDL level is low will result in buildup in the blood. This will facilitate acetylation and cholesterol leakage from the blood vessel, causing xanthelasma.<sup>2,6</sup>

Akyus in 2016 reported a higher triglyceride level in xanthelasma than in the control group.<sup>33</sup> The study also reported significantly higher triglyceride levels in xanthelasma patients compared to the control group (154 versus 101 mg/dl,  $p = 0.01$ ). In this study, there was a not significant rise in the triglyceride level between the xanthelasma patients and the controls subjects. Increased serum cholesterol and LDL level correlated to xanthelasma ( $p < 0.05$ ). However, a decreased serum HDL and increased serum triglycerides level were not proven to be associated with xanthelasma.

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