Correlation between serum lipid profile and acne vulgaris severity

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Abstract. Minimal reports are available on the relation between blood lipids and acne vulgaris (AV). Sebaceous glands are the key roles in AV pathogenesis, while the sebum lipids in sebaceous glands are one of the main factors for AV development. Recently, any changes in the proportions of blood lipoprotein are known to be related to AV incidence. The study was conducted to determine the correlation between serum lipid profile and AV severity. Sixty-two study participants, who met the inclusion criteria based on the consecutive sampling method, were enrolled in the study. The levels of lipid profile were measured and the AV severity was determined by Lehmann criteria. Results showed that the majority of participants had moderate AV (56.5%) and there was an increase in LDL-C levels (54.8%). There was a statistically significant correlation between TC levels and AV severity \( p=0.001; \ r=0.332 \) as well as a strong correlation between LDL-C levels and AV severity \( p=0.000; \ r=0.622 \). The study also found a tendency of HDL-C levels decrease, followed by increased AV severity, and vice versa \( p=0.041; \ r=-0.229 \). The study suggested that there was a significant correlation between serum lipid profile and AV severity.

1. Introduction

Acne vulgaris (AV) is a chronic inflammatory of pilosebaceous units. It is characterized by seborrhoea, comedones, papules, pustules, nodules, pseudocyst, and possible scarring. Comedones are the pathognomonic lesions of AV. Predilection of AV is in area with a high density of sebaceous glands, such as the face, upper anterior and posterior trunk [1,2]. The pathogenesis of AV is multifactorial. Four main factors which play important roles in AV pathogenesis are (1) follicular epidermal hyperproliferation, (2) inflammation, (3) Propionibacterium acnes \((P.\ acnes)\) activity, and (4) increased sebum production [3]. Some factors related to AV are family history of AV, increased body mass index (BMI), psychological stress and oily skin type [4].

Currently it is known that altered proportion of blood lipoprotein is associated with AV incidences. The increase of cholesterol levels leads to the elevation of androgen levels which increases sebum and keratinocyte hyperproliferation on AV patients. Sebaceous gland has the ability to synthesize enzymatically androgen \textit{de novo} from cholesterol or dehidroepiandrosterone (DHE). The latest data indicated a strong association between increased sebaceous lipid synthesis and inflammation, that was considered important in the initiation of AV lesion [5,6].

Studies on blood lipid profile and AV were not widely reported and they showed varied results. Akawi et al., demonstrated that there was a significant decrease in high density cholesterol (HDL-C)
levels compared to the control group in AV patients. Their study also revealed that severe AV patients had an increase in triglyceride and low-density cholesterol (LDL-C) levels compared to the control group [7]. Cunha et al., reported the increase of total cholesterol (TC) and LDL-C levels in patients with moderate to severe AV [8]. The elevation of TC, LDL-C and serum lipoprotein levels in moderate and severe AV patients were significantly higher than in control groups was demonstrated in a study by Jiang et al [9]. Study by Vergani et al. indicated a significant decrease of HDL-C levels in patients with severe AV, while significant differences in TC and triglyceride levels between AV patients and normal controls were not observed [10]. The present study was conducted to determine the correlation between serum lipid profile (LDL-C, HDL-C, TC and triglyceride) and AV severity.

2. Methods

2.1. Study participants

The study is an observational, analytical laboratory study with cross-sectional study design. The study was conducted in May to June of 2016 at the Cosmetic Dermatology Clinic of Dr. Mohammad Hoesin Hospital in Palembang. Ethical approval was obtained from the ethics committee of Dr. Mohammad Hoesin Hospital and Medical Faculty of Sriwijaya University in Palembang.

Study population was AV patients who attended Dermatology and Venereology (DV) Outpatient Clinic of Dr. Mohammad Hoesin Hospital Palembang during study period. Study participant was the population who met inclusion and exclusion criteria based on the consecutive sampling method. Criteria for inclusion in this study were AV patients aged from 12 to 35 years, patients and/or guardian of patients that were willing to participate in study by signing the approval form to join study and the informed consent form. The exclusion criteria were pregnant and nursing, suffered from certain skin conditions such as seborrheic dermatitis, psoriasis vulgaris, rosacea or atopic dermatitis which could affect sebum and serum lipids, under systemic and topical medications for AV (the minimum of a month prior to the study), under hormonal and estrogen contraceptives (the minimum of three months prior to the study), under antihyperlipidemic drug therapy (the minimum of a month prior to the study), and suffered from human immunodeficiency virus infection.

2.2. Analyzed parameters

During the study period, sixty-two AV participants underwent measurements of serum lipid profile and AV severity (determined by Lehmann criteria). According to Lehmann criteria, lesion count was used to classify AV into three groups; mild, moderate and severe acne. Based on the number of comedo, inflammatory lesion and total lesion count, AV was classified as: <20 comedones, or <15 inflammatory lesions, or total lesion count <30, mild; 20-100 comedones, or 15-50 inflammatory lesions, or total lesion count 30-125, moderate; >5 cysts, or total comedo count >100, or total inflammatory count >50, or total lesion count >125, severe [11]. The grading scale classified AV appropriately and had been used in the Clinical Practice Guideline of Indonesian Dermatology-Venereologist.

Participants were fasting for 8 to 12 hours at the time of blood withdrawal. Serum lipid profiles were determined using spectrophotometry method. Serum lipid profile levels were estimated by commercially available enzymatic colorimetric tests according to the manufacturer recommended procedure. Serum lipid concentrations were measured using Advia1800® Clinical Chemistry System (Siemens, Erlangen, Germany). The normal ranges for the serum lipid profile were based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline [12].

2.3. Statistical analysis

Covariables assessed in the study were as follow: age, gender, education, occupation, BMI and skin types (determined by sebum levels using a Sebumeter®). Statistical analysis was performed using Statistical Programme for Social Sciences (SPSS) 22.0 software (SPSS Inc., Chicago, USA). Descriptive data were expressed as number of participants (n), percentage or mean ± standard deviation. The bivariate analysis determined the correlation between serum lipid profile and AV severity. Both dependent and independent variables were categorical variables; therefore the strength
of correlation was assessed by Somers’D correlation test. Correlation test result was showed as the correlation coefficient r. The p-value was considered significant as p <0.05.

3. Results
Sixty-two study participants, aged from 15 to 35 years, were enrolled in the study. The proportion of female participants was higher than male participants (80.6% vs 19.4%). The mean age of participants was 22.25 ± 4.605. The characteristics of participants can be seen in Table 1.

| Characteristics                | n (%)  |
|--------------------------------|--------|
| Gender                         |        |
| Male                           | 12 (19.4) |
| Female                         | 50 (80.6) |
| Skin type (sebum secretion)    |        |
| Oily (>220µg/cm²)              | 49 (79) |
| Normal (100-220µg/cm²)         | 9 (14.5) |
| Dry (<100µg/cm²)               | 4 (6.5) |
| BMI                            |        |
| < 18.5 (underweight)           | 9 (14.5) |
| 18.5-24.9 (normoweight)        | 46 (74.2) |
| 25%-29.9 (overweight)          | 6 (9.7) |
| ≥ 30 (obese)                  | 1 (1.6) |

Table 1. Characteristics of study participants.

| AV severity     | n (%)  |
|-----------------|--------|
| Mild            | 22 (35.5) |
| Moderate        | 35 (56.5) |
| Severe          | 5 (8.1) |
| Total           | 62 (100) |

Table 2. AV severity characteristics of study participants.

Table 3. Lipid profile distribution frequency of study participants.

| Lipid Profile | Triglyceride levels | TC levels | LDL-C levels | HDL-C levels |
|---------------|---------------------|-----------|--------------|--------------|
|               | N²                  | Border -line high | High | N² | Border -line high | High | Border -line high | High | N² Low | High |
| n             | 59                  | 3           | 48         | 10   | 4 | 28         | 20   | 9 | 4 | 1 | 44 | 6.5 | 22.6 |
| %             | 95.2                | 4.8         | 77.4       | 16.1 | 6.5 | 45.2       | 32.3 | 14.5 | 6.5 | 1.6 | 71.0 | 6.5 | 22.6 |

As shown in table 2, in our study, most of study participants had moderate AV (56.5%), followed by mild (35.5%) and severe AV (8.1%), according to Lehmann criteria. In table 3, we demonstrated that most of participants had normal triglyceride (95.2%), TC (77.4%) and HDL-C (71%) levels, while there was an increase in LDL-C levels (54.8%).

As shown in table 4, there was a statistically significant correlation between AV severity and TC levels ($p = 0.001; r = 0.332$). Our study also demonstrated a strong correlation between LDL-C levels and AV severity ($p = 0.000; r = 0.622$) as shown in table 5.

We noticed that there was a tendency of HDL-C levels decrease, followed by increased AV severity, and vice versa ($p = 0.041; r = -0.229$), as demonstrated in table 6. However, in the study, the correlation between triglyceride levels and AV severity was not observed (table 7).

4. Discussions
The sources of sebum lipid are derived from de novo synthesis of sebaceous gland and blood lipid [5]. There are three main types of blood lipids, i.e. triglycerides, phospholipids and cholesterols [13]. Lipids circulate in the blood embedded in specialized complex molecules structures mostly
synthesized in the liver, known as lipoproteins [14]. Sebaceous gland has the ability to segregate dietary cholesterol and fatty acids from their environment, called endogenously derived lipid sources. The blood lipid and lipoprotein levels may play a role in determining the composition of sebum lipid. The uptake of circulating lipid by sebaceous glands was shown in Downing et al. study, which found 20% decrease of free fatty acids in sebum while in fat diet restriction. These results indicated that circulating lipid uptake was an important stage in sebaceous lipids production [15,16]. However, there is no conclusive study clarifying to which extent the sebaceous gland synthesizes sebum lipids de novo, uptakes blood preformed lipids, or modifies lipid precursors [5].

**Table 4. Correlation of TC levels and AV severity.**

| TC levels       | AV Severity | Total | p-value* | r^b |
|-----------------|-------------|-------|----------|-----|
| Normal          | Mild        | 21    | 25       | 2   | 48  |
|                 | Moderate    | 6     | 1        |     | 10  |
|                 | Severe      | 0     | 4        |     | 4   |
|                 | Total       | 22    | 35       | 5   | 62  |

*p-value <0.05 was considered statistically significant.

**Table 5. Correlation of LDL-C levels and AV severity.**

| LDL-C levels   | AV Severity | Total | p-value* | r^b |
|---------------|-------------|-------|----------|-----|
| Normal        | Mild        | 21    | 7        | 0   | 28  |
|               | Moderate    | 0     | 18       | 2   | 20  |
|               | Severe      | 0     | 7        | 2   | 9   |
| High          |             | 1     | 2        | 1   | 4   |
|               | Total       | 22    | 35       | 5   | 62  |

*p-value <0.05 was considered statistically significant.

**Table 6. Correlation of HDL-C levels and AV severity.**

| HDL-C levels | AV Severity | Total | p-value* | r^b |
|--------------|-------------|-------|----------|-----|
| Low          |             | 0     | 4        | 0   | 4   |
| Moderate     |             | 14    | 26       | 4   | 44  |
| High         |             | 8     | 5        | 1   | 14  |
| Total        |             | 22    | 35       | 5   | 62  |

*p-value <0.05 was considered statistically significant.

**Table 7. Correlation of triglyceride levels and AV severity.**

| Triglyceride levels | AV Severity | Total | p-value* |
|---------------------|-------------|-------|----------|
| Normal              |             | 22    | 32       | 5       | 59    |
| Borderline high     |             | 0     | 3        | 0       | 3     | 0.097 |
| Total               |             | 22    | 35       | 5       | 62    |

*p-value <0.05 was considered statistically significant.

Sebaceous glands express two receptors that are involved in circulating lipid uptake, i.e. LDL and fatty acids transport protein (FATP) receptors, mainly FATP4 receptors. Sebaceous glands also express lipoprotein lipase enzymes, which can bind and breakdown serum lipoproteins into fatty acids [5]. Blood lipid profiles were influenced by many factors, namely, genetic, different nutritional status, lifestyle and diet [17]. Dyslipidemias are disorders of lipoprotein metabolism that manifested by elevation of the TC, LDL-C, and triglyceride levels and a decrease in HDL-C levels [18]. The increase
of LDL-C levels on patients with AV was recorded to prior studies reported by Akawi et al., Cunha et al., and Jiang et al [7,8,9]. Similarly, our study revealed the increase of LDL-C levels on 54.8% of study participants. However, most of study participant had normal TC, HDL-C, and triglyceride levels.

The LDL-C, the major lipoprotein cholesterol circulating in the body, is used by extrahepatic cell for synthesis of cell membranes and steroid hormones [19]. Increased serum cholesterole levels may increase the amount of sebum and keratinocyte proliferation through androgen activity. The androgenic skin has higher androgen receptor density and 5 α-reductase activity than normal skin. On the contrary, antianandrogens would decrease sebaceous lipids synthesis and reduce AV incidences [5,20].

In our study, Somers’ D correlation test result showed a significant weak correlation between TC levels and AV severity, and a significant strong correlation between LDL-C levels and AV severity. Similarly, the study by Akawi et al. also showed a significant difference in serum LDL-C levels (p =0.000) between patients with severe AV and normal controls. Meanwhile, the study by Jiang et al. resulted in significantly higher levels of TC, LDL-C, and serum lipoproteins in severe and mild AV patients compared to normal controls (p <0.05) [7,9].

Cholesterol enters the cells via the LDL receptor-mediated endocytosis, leading to HMG-CoA reductase transcription and translation inhibition and also the stimulation of enzyme degradation. It is known that HMG-CoA reductase is regulated by the cholesterol levels in the sebaceous gland environment so that the increase of blood cholesterol levels might influence squalene levels in the sebum. Squalene is an intermediate product in the biosynthesis of cholesterol and is a characteristic human sebaceous lipid. It also can be found in the blood as a consequence of lipid leakage from the cholesterol biosynthesis. However, squalene levels in sebum are more abundant than those in blood. Likely, sebocyte has evolved a mechanism that interrupts the cholesterol biosynthesis and promotes squalene accumulation. The existence of six double chains in the chemical structure allows squalene to easily undergo photo-oxidation process producing squalene mono-hydroperoxide as the main product which has pro-inflammatory activity [5,21].

Lipid peroxidation levels were associated with the formation of comedones. Motoyoshi et al., demonstrated that increased lipid peroxide levels could induce follicular infundibulum epithelium hyperplasia and hyperkeratosis as well as increased sebaceous gland proliferation. Such consequence was mainly due to comedogenic effect of squalene mono-hydroperoxide. In vitro study by Ottaviani et al., suggested that lipid peroxides not only could induce keratinocyte proliferation, but also increase the release of inflammatory mediators such as interleukine (IL)-6. Such finding showed the pro-inflammatory lipid peroxides activity. This inflammatory reaction was a part of inflammatory lesions development of AV. The role of lipid peroxidation in AV development is reinforced by an examination on skin surface and comedones lipids of AV patients where abundant amount of squalene mono-hydroperoxides are in [21,22].

Lipid peroxides also trigger the peroxisome proliferator-activated receptors (PPARs) activation, receptors that play a role in lipid regulation, lipoprotein metabolism, inflammatory response, epidermal cell proliferation and differentiation as well as sebaceous gland cell apoptosis. The PPARs are abundantly present in human sebaceous glands. Rosenfield et al., suggested that among various types of PPARs, PPARα and PPARγ were the most associated receptor with lipid synthesis. These receptors are known to play a role in increased sebum production. A significant increase in sebum of patients with hyperlipidemia who had fibrate (PPARα agonist) and in sebume of type II diabetic patients who had thiazolidinedion (PPARγ agonist) was reported by Trivedi et al [6,20,24]. The elevation of lipid peroxides stimulates lipoxygenase (LOX) enzymes release. Sebocytes release LOX which competes against desaturase enzymes and converts linoleats into arachidonic acids, thus triggering inflammatory cascade [6].

The cholesterol transport from non-hepatic cells to the liver involves HDL particles in a process, namely, reverse cholesterol transport [19]. Our study demonstrated a significant correlation between HDL-C levels and AV severity in a negative correlation manner. Such outcome showed a tendency that the lower the levels of HDL-C, the higher the AV severity, and vice versa. These results were similar to a study by Akawi et al. They found a significant decrease of HDL-C levels along with the increase of AV severity (p =0.000) [7]. Nevertheless, the outcome correlation in our study was weak correlation. The weak correlation between HDL-C levels and AV severity could be explained in the
manner of HDL-C not being uptaken by sebaceous glands for sebum synthesis. Otherwise, HDL-C would re-uptake lipids in peripheral organs back to liver and then were excreted as cholesterol or bile salts [25].

Besides the passive diffusion mechanism, free fatty acids are mostly translocated to the cytoplasm through an active mechanism, involving FATP receptors [26]. Free fatty acids were found to increase in the skin surface lipids of AV patients. Those fatty acids were derived from triglycerides lipolysis and involved in inflammatory process on AV [27]. Arachidonic acid, a polyunsaturated omega-6 fatty acid, helps to perpetuate the inflammatory cascade in AV. The increase of arachidonic acid cascade in sebum induces an increase in synthesis of IL-6, IL-8, proinflammatory lipids, as well as the production of leukotriene (LTB)-4 that stimulates pro-inflammatory cytokines production and keratinocytes hyperproliferation in AV [24,28]. Acne medication with 5-LOX inhibitor has been proven to reduce inflammatory process within sebaceous glands and sebaceous lipids synthesis, thus reducing AV lesions. The 5-LOX enzyme is one of the strongest PPAR ligands which catalyses LTB-4 [29].

However, in our study, the correlation between triglyceride levels and AV severity was not observed. Such result was similar to that of Vergani et al., in which a significant difference in triglyceride levels between AV patients and controls (p >0.05) was also not found [10]. Several studies suggested that inflammatory markers increase as the ratio of omega-6 to omega-3 fatty acids increase. Omega-6 fatty acids are precursors to pro-inflammatory mediators and have been associated with AV development [30]. Those findings indicated the important role of ratio between omega-6 fatty acid and omega-3 fatty acid on AV patients.

Despite the study being done with a proper methodology, the study was still constricted by a few limitations. First, the role of androgen in AV severity in the study was only found in serum cholesterol increase and there was no examination of testosterone levels to find out any correlation between AV severity and the increase of serum cholesterol and androgen. The limitation becomes a setback in the study as the status of hyperandrogenism in study participants could not be determined; therefore the correlation between androgen and serum cholesterol affecting AV severity could not be analyzed. Second, there was no examination of sebum lipid profile so that the study could not determine the correlation between serum lipid profile and sebum lipid profile which could affect AV severity. Further study on serum lipid profile and AV with androgen levels and sebum lipid profile examination in AV patients is required. However, facial sebum measurement of study participants was conducted using a Sebumeter® (SM 815, C-K electronics, Cologne, Germany). The group of acne patients excretes more sebum than normal individuals. Increased sebum secretion is one of important factors in the pathophysiology of AV [3]. Our study demonstrated oily skin type as the most common among participants. This finding is in agreement with our study results demonstrating increased LDL-C levels in most participants and a significant correlation between LDL-C levels and AV severity.

Acne is an inflammatory disease due to interference with the natural cycle of sebaceous follicles. Its pathogenesis is complex and is dependent on the interplay of genetic predisposition and various mechanisms including androgen, PPAR ligands, and other factors. Pro-inflammatory lipids and cytokines or chemokines appear to act as inflammatory mediators on AV [20,21]. Serum cholesterol levels might affect AV severity by increasing sebum lipids and lipid peroxides thus triggering follicular epidermal and sebaceous gland hyperproliferation and inflammation in AV. Dietary saturated fatty acids may increase LDL-C levels, meanwhile, high levels of polyunsaturated omega-3 fatty acids have been shown to decrease inflammatory factors and prevent sebaceous follicles hyperkeratinisation [30,31]. Those findings indicated the importance of diet habit as one of possible factors influencing the AV severity.

5. Conclusions
In conclusion, our study showed a significant correlation between serum lipids (LDL-C, HDL-C, and TC) and AV severity, thus the examination of serum lipids could be considered as an additional examination for AV treatment, moreover, a diet modification in AV patients with dyslipidaemia could be considered.
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