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# The Relationship of Salivary Free Testosterone Concentration with Acne Vulgaris

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**Abstract:** Background: Acne Vulgaris (AV) is a chronic inflammatory and multifactorial disease involving the pilosebaceous unit. Androgen hormone plays an important role in the pathogenesis of acne. Objective: This study aims to determine the relationship of free testosterone concentration with the severity of acne vulgaris. Methods: This is an observational study using cross sectional design. This study conducted in Dr. Wahidin Sudirohusodo hospital, Hasanuddin University hospital, and other hospital networks and Prodia laboratory in Makassar starting from January until February 2015. The study samples are 42 patients who met the study criteria. There are 32 patients with AV who have been diagnosed clinically and 10 patients with non AV as a control group. Results: The free testosterone concentration and sebum levels in the AV group are higher compared to the control group ( $p < 0.005$ ). This study obtained that there is no significant difference of free testosterone concentration and sebum levels according to the AV levels ( $p > 0.005$ ), but there is a correlation between the free testosterone concentration with the increased of sebum levels. It is mean that even the free testosterone concentration and sebum levels are increased, the acne vulgaris is not necessarily severe, but the increased of free testosterone concentration makes the sebum levels increased. Conclusions: The free testosterone concentration and sebum levels are higher in the acne vulgaris group than the control group. There is no significant relationship of free testosterone concentration with acne vulgaris with  $p > 0.05$ .

**Keywords:** Free Testosterone, Sebum Levels, Acne Vulgaris

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## 1. Introduction

Acne vulgaris (AV) is a chronic inflammatory disease on pilosebaceous follicles that are often experienced by teenagers and adults. It is marked by the blackheads, papules, pustules and nodules and scarring also. Acne vulgaris is usually on the chest, face, shoulders, arms and back<sup>(1)</sup>.

The aetiology of AV until now is still not certain yet. However, generally the experts assumed that AV is a multifactorial disease, characterized by impaired differentiation and the increase in sebaceous follicles keratinization, the increase activity of sebaceous glands and hyperseborrhoea, and propionibacterium acne hyper colonization<sup>(2, 3)</sup>.

Several studies stated that the AV prevalence in several countries reaches 70-78%.<sup>(4)</sup> The number of the AV's patient in 2008 is 7.8% of all visits in Dermatology Polyclinic of Dr. Wahidin Sudirohusodo hospital.

The AV classification is based on the combined acne severity classification, which divided into mild, moderate, and severe acne. The AV is categorize as severe if the cyst count is  $>5$ , or total comedones count  $>100$ , inflammatory lesions  $>50$ , or total lesion count  $>125$ . Moderate AV comedones count is 20-100, inflammatory lesions 15-50 or total lesion count is 30-125, while the mild AV comedones is  $<20$ , inflammatory lesions  $<15$  or total lesion count is  $<30$ .<sup>(5)</sup>

Various studies show the important of androgens on AV pathogenesis. Androgens significantly increase the size of the

sebaceous gland and stimulate the production of sebum. Moreover, it stimulates the proliferation of keratinocytes in the sebaceous gland ducts and macro-infundibulum.<sup>(6)</sup> Acne vulgaris began to appear coincide with the adrenarche occurs, that is the age when adrenal gland produces the dehydroepiandrosterone sulfate hormone, a precursor of testosterone. Hyperandrogenism associated with the increased of sebum production and the incidence of severe acne.<sup>(7)</sup>

Measurement of free testosterone in saliva shows a very high correlation with the concentration of free testosterone in serum.<sup>(8)</sup> Several studies suggest the examination of free testosterone through saliva because it is more sensitive detection for hyperandrogenism.<sup>(9)</sup>

Based on the above stated, we conducted this study to assess the relationship of free testosterone concentration in saliva with acne vulgaris.

## 2. Materials and Methods

This was an observational study using the cross sectional

design, which the entire study variable are measured in the same period of time. This study was conducted in Makassar, South Sulawesi in Dr. Wahidin Sudirohusodo hospital, Hasanuddin University hospital and other hospital networks and Prodia of Makassar, starting from January until February 2015. Written informed consent was obtained from the patients' parents or legal guardian following full and detail explanation regarding the study's protocol.

This is a cross sectional study to assess the relationship of free testosterone concentration with the severity of acne vulgaris. The samples are calculated by using the Mann Whitney U from Sidney Siegel 3 and 1. We obtained 42 patients that met the study criteria, which are 32 patients with AV who were clinically diagnosed and met the sample criteria, while the 10 patients are non AV as a control group. The inclusion criteria of this study are the acne patient based on the Combined Acne Severity Classification assessed by a dermatologist and pathologist. The exclusion criteria are acne vulgaris patient, who are using the contraception hormone, are pregnant and lactating, having oral infection, and refused to participate.

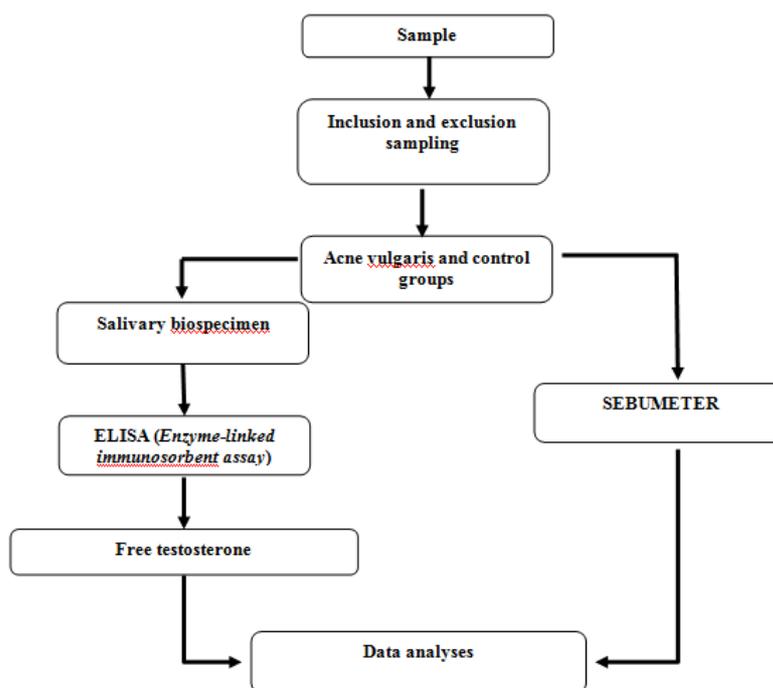


Figure 1. Study flow scheme.

The patients that met the study criteria then filled the questionnaire about their personal data and medical history, and picture of lesions location on their faces was taken using the digital camera. The data was analyzed by using the Statistical Package for Social Science (SPSS) version 22. Statistical test used are the correlation of Spearman test and Mann Whitney U test with significance level  $p < 0.05$ .

Besides, we also obtained the biospecimen of each samples. The biospecimen intake are including the salivary specimen, testosterone examine, and the sebumeter measurement. The salivary sample both of the AV and control group are intake by using the *Salimetrics Oral Swab* (SOS),

then it is frozen at or under  $-20^{\circ}\text{C}$  in 4 hours of collecting time. While, the measurement of the entire patients in order to assess the sebumeter using the sebumeter tool of SM 815 manufactured of Chaurage & Khazake Electronic GmbH Jerman in 2003.

## 3. Results

In table 1 show that we obtained 42 samples of study that are divided into 32 samples in AV group and 10 samples in non AV group with age range from 12-35 years, and the mean value is 19 years. In the non AV group, there are 5 patients in

range of age 12-19, either in the aged of 20-35 years. The mean value of free testosterone concentration on AV group is 0.713 nmol/L, and the non AV group mean value is 0.420 nmol/L. The sebum level is varied from 23-299  $\mu\text{g}/\text{cm}^2$ , with mean value in the AV group is 184.25  $\mu\text{g}/\text{cm}^2$  and the mean value of non AV group is 60.60  $\mu\text{g}/\text{cm}^2$ .

**Table 1.** Sample characteristics.

Sample characteristics		Acne Vulgaris	Non Acne Vulgaris
Age	n	22	5
12-19 Years	%	68.8%	50.0%
20-35 Years	n	10	5
	%	31.3%	50.0%
Total	n	32	10
	%	100%	100%
Free testosterone concentration mean (nmol/L)		0.713	0.420
Sebum levels mean ( $\mu\text{g}/\text{cm}^2$ )		184.25	60.60

Source: primer data

Table 2 presents the free testosterone concentration in the AV group with 0.713 is significant higher compared to the non AV group with 0.420 ( $p < 0.05$ ). The sebum levels in the AV group with 184.25 were also has a significant higher compared to the non AV group with 60.60 ( $p < 0.05$ ).

**Table 2.** Mean comparison of free testosterone and sebum levels according to AV and Non AV groups.

Variable	Group	n	Mean	SD	P
Free Testosterone concentrate (nmol/L)	AV	32	0.713	0.445	0.012
	Non AV	10	0.420	0.192	
Sebum levels ( $\mu\text{g}/\text{cm}^2$ )	AV	32	184.25	63.743	0.000
	Non AV	10	60.60	36.897	

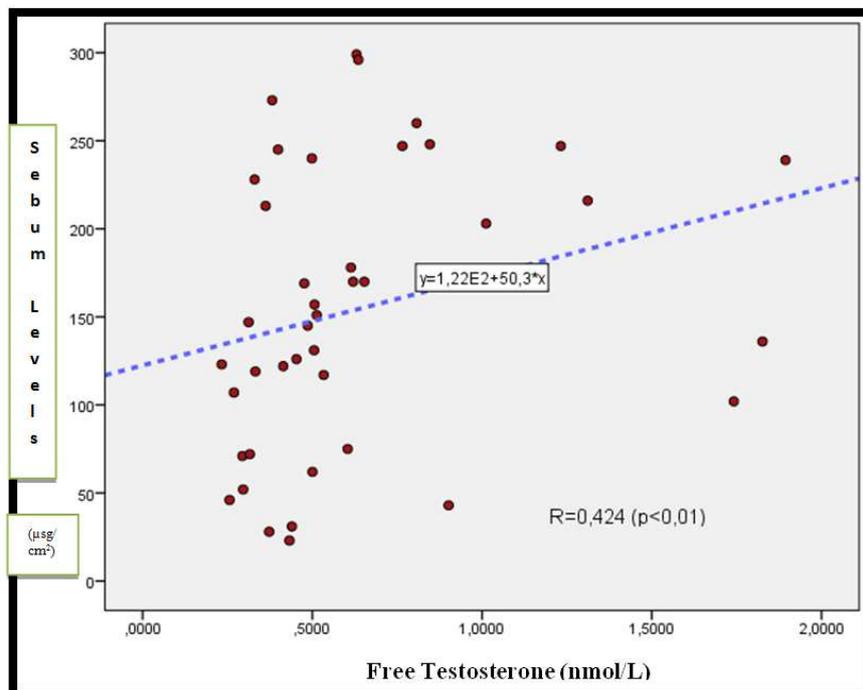
Mann-Whitney test

Table 3 show there is no significant difference of free testosterone concentrate according to AV levels ( $p > 0.05$ ). Moreover, there is also no significant difference of sebum levels according to the AV levels ( $p > 0.05$ ). This indicates that both of the free testosterone concentration and sebum levels have no significant correlation with the AV levels.

**Table 3.** The comparison of free testosterone concentrate and sebum levels according to AV levels.

Variable	Acne levels	n	Mean	SD	P
Free testosterone concentrate (nmol/L)	Mild	15	0.720	0.531	0.55
	Moderate	17	0.706	0.369	
Sebum levels ( $\mu\text{g}/\text{cm}^2$ )	Mild	15	175.40	64.781	0.54
	Moderate	17	192.06	63.735	

Mann-Whitney test



**Figure 2.** The correlation between free testosterone concentrate with sebum levels.

According to the result of the Spearman correlation test in figure 2, we obtained that is a significant positive correlation between the free testosterone concentrate with the sebum levels ( $r = 0.424$  and  $p < 0.01$ ). This finding shows that the

higher of free testosterone concentrate, the sebum levels are also higher. The correlation value between both variable is mild. Even though there is a correlation between the free testosterone concentration and sebum levels, but both of it

did not have a significant correlation to the acne vulgaris levels.

## 4. Discussion

Acne Vulgaris is often found by the dermatologist in teenager and usually continued to adult with age range from 11-30 years, with the incidence peak at the age of 18 years.<sup>(1, 10, 11)</sup> Significantly, the androgens increased the sebaceous gland and stimulate the production of sebum. Moreover, it stimulates the keratinocytes proliferation on sebaceous gland and acro-infundibulum.<sup>(6)</sup> Sebaceous glands begin to swell in the presence of androgen stimulus around the age of 7-8 years, which resulted in increased excretion of sebum.<sup>(12)</sup> The imbalance of sebum production and its secretion ability will result in the accumulation of sebum in the hair follicle, causes formation of mikrocomedo which then followed by the inflammatory process and becoming inflamed.<sup>(12, 13)</sup>

This study obtained the free testosterone concentration in the AV group with 0.713 is significant higher compared to the non AV group with 0.420 ( $p < 0.05$ ). The sebum levels in the AV group with 184.25 were also has a significant higher compared to the non AV group with 60.60 ( $p < 0.05$ ). Research by Lawrence et al. obtained the free and total testosterone concentrate on plasma significantly increased on the male and female of AV group.<sup>(8)</sup> According to the research by Mustikawati et al. the relationship of cyp17 gene polymorphism and increasing sebum levels in AV found that sebum levels of severe AV is two times higher than the mild AV group.<sup>(14)</sup> In several researches, AV patients have a higher level free testosterone, DHEAS, 5 $\alpha$ -reductase, and androgen receptors in the sebaceous glands in circulation than patients without AV. However, it is generally believed, that the sebaceous glands hypersensitivity to androgens are the underlying causes of AV.<sup>(15)</sup> The sebum secretion is hormonally regulated. This hormone will still affect the activity of the sebaceous glands until adulthood. In female, sudden increase in luteinizing hormone follows the ovulation accelerates sebaceous gland activity.<sup>(16)</sup> Approximately 85% of women reported a worsening of AV symptoms during the premenstrual period.<sup>(17)</sup> The most common cause of this situation is the alteration in androgen skin receptor response to hormonal changes in the physiology of the menstrual cycle, which is related to the emergence of inflammatory lesions and increasing sebogenesis.<sup>(18)</sup>

In this study, it was found no significant difference of free testosterone concentrate and sebum levels according to the degree of AV. These result is correspond with the research in Iraq by Sulaiman that obtained no positive correlation between the serum androgen hormone levels with the AV levels.<sup>(19)</sup> Acne vulgaris is a multifactorial disease. Sebum is one of the AV pathogenesis, and many men do not have AV despite high levels of androgen hormones. In addition, many people with high sebum production do not experience AV.<sup>(6)</sup>

This study obtained a positive correlation between free testosterone concentrate and sebum levels with  $r = 0.424$  ( $p < 0.01$ ). It means that there is a significant correlation

between free testosterone concentrate and sebum levels. The higher the free testosterone level the higher the sebum levels will be, but both of the free testosterone concentration and sebum levels did not have a significant relationship with AV levels.

Androgen is one of the hormones involved in the pathphysiology of acne. Most of the circulating androgens are produced by the adrenal glands and gonads. Besides synthesized by endocrine organs, this hormone is also produced by the skin; the place where all the enzymes needed to convert cholesterol to steroid is placed. The mechanism by androgens increase the activity of sebaceous glands and hypertrophy is still unclear but there is scientific evidence that supports this relationship. Testosterone and dihydrotestosterone (DHT) binding the nuclear androgen receptor, which then interacts with deoxyribonucleic acid (DNA) in the nucleus of sebaceous cells and ultimately regulate genes involved in cell proliferation and lipogenesis. Although the target genes may not be known, but it is suspected that they might be including genes that encode growth factors and lipogenic enzymes. Peroxisome proliferators-activated receptor (PPAR) ligands may also be involved in the regulation of lipid metabolic genes.<sup>(15)</sup>

The result of this study concludes that there is no correlation between free testosterone concentration and sebum levels on the severity of the AV. However it was found that there is a correlation between free testosterone concentrations with the sebum levels, which means the higher concentrate of free testosterone, the higher levels of sebum.

## Abbreviation

AV: Acne Vulgaris

Non AV: Non Acne Vulgaris

DHEAS: Dehydroepiandrosterone sulfate

DHT: Dihydrotestosteron

DNA: Deoxyribonucleic acid

PPAR: Peroxisome proliferators-activated receptor

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