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## High plasma H<sub>2</sub>O<sub>2</sub> level and low plasma catalase level as risk factors for acne vulgaris

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### ABSTRACT

**Background:** In this recent time, ROS and oxidative stress have been said to play an important role in the pathogenesis of inflamed acne lesions. One example of ROS produced by neutrophil through phagocytosis is H<sub>2</sub>O<sub>2</sub>. Nevertheless, there is an enzymatic antioxidant which catalyses H<sub>2</sub>O<sub>2</sub> called catalase. Imbalance of free radicals and antioxidants due to excessive ROS formation promotes the state of oxidative stress and inflammation of the acne lesion.

**Objective:** This study aimed to determine plasma H<sub>2</sub>O<sub>2</sub> and catalase level as a risk factor for acne.

**Methods:** This matched-pair case-control observational analytic study involving 38 patients with acne and 38 patients without acne. Sampling was done using consecutive sampling which fulfils the inclusion and exclusion criteria and followed by matching with age

and gender. H<sub>2</sub>O<sub>2</sub> and catalase level measured on both groups. The analysis was done using SPSS.

**Results:** H<sub>2</sub>O<sub>2</sub> mean level in the case and control group, respectively 0.68 ± 0.03 and 0.42 ± 0.04 μmol/ml. High H<sub>2</sub>O<sub>2</sub> level was determined from cut-off point >0.62 μmol/ml. High H<sub>2</sub>O<sub>2</sub> was a statistically significant risk factor for acne vulgaris (p<0.001; 95% CI: 4.59-40.62; OR: 13.67). The mean level of catalase in the case and control group respectively 0.48 ± 0.06 and 0.74 ± 0.07 U/ml. Low catalase level was determined from the cut-off point <0.58 U/ml. Catalase was significant risk factor for acne vulgaris (p<0.001; 95% CI: 5.18-77.21; OR: 20.00).

**Conclusion:** High levels of H<sub>2</sub>O<sub>2</sub> plasma and low levels of catalase plasma is a risk factor of acne vulgaris.

**Keywords:** acne vulgaris, H<sub>2</sub>O<sub>2</sub>, hydrogen peroxidase, catalase

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### INTRODUCTION

Acne vulgaris is a chronic inflammatory and obstructive skin disease which occurs on the pilosebaceous unit commonly found in teenagers and young adults. Acne vulgaris can be classified to comedonal, papulopustular and nodulocystic types of lesion. Papulopustular and nodulocystic type of acne forms a group of the inflammatory type of acne vulgaris.<sup>1,2</sup> In some cases, acne may reside by itself, but it may also leave scars which will last.<sup>3</sup> The incidence of acne vulgaris is around 85% and mostly found at a younger age.<sup>4</sup> Acne vulgaris is common in Indonesia and is found 85-100% during the lifetime of an individual.<sup>5</sup> A retrospective study of acne vulgaris prevalence in adult women above 25 years of age conducted in Department of Venereology of Sanglah General Hospital on the period of January 2013 to December 2014. Results showed that 4.71% of acne vulgaris was caused by hormonal instability.<sup>6</sup>

The pathogenesis of acne is complex and multifactorial. Currently, four main factors of acne have been identified, and these include an increase of sebum production, epidermal follicular

hyperproliferation, Propionibacterium acnes bacteria colonisation, and inflammation. Lately, there has been a growing interest in comprehending the roles of reactive oxygen species and oxidative stress in inflammatory acne pathogenesis.<sup>7,8</sup> Patients with an inflammatory type of acne had a 43% higher H<sub>2</sub>O<sub>2</sub> level compared to healthy individuals. The elevation of H<sub>2</sub>O<sub>2</sub> level has been used as a marker of oxidative stress condition.<sup>9</sup>

Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) is a ROS product of neutrophilic phagocytosis. Antioxidants, the protective factor of oxidative stress, can be classified into enzymatic and non-enzymatic antioxidants. Catalase is a hydroperoxides enzyme which catalyses H<sub>2</sub>O<sub>2</sub> or other organic peroxides.<sup>9</sup> Overproduction of ROS which exceeds the ability of antioxidants can trigger a condition known as oxidative stress. Increase of ROS production may cause the breakdown of follicular walls thus ultimately resulting in inflammatory acne lesions.<sup>7,8</sup>

The defensive system of antioxidants such as SOD and catalase keep cellular redox stability by controlling ROS production. This could happen due to the ability of SOD to turn superoxide dismutase to H<sub>2</sub>O<sub>2</sub>, followed by catalase catalysing H<sub>2</sub>O<sub>2</sub> to water.

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The change of redox stability due to an increase of ROS production or the decrease of antioxidants may contribute to oxidative stress.<sup>8</sup> Decrease of catalase may be caused by the accumulation of H<sub>2</sub>O<sub>2</sub> around the lesion site. This was supported with the findings of the increase of H<sub>2</sub>O<sub>2</sub> levels on acne patients.<sup>11</sup>

There has not been a study done to comprehend the roles of both oxidants and antioxidants shown by high H<sub>2</sub>O<sub>2</sub> plasma levels and low catalase plasma levels on patients with acne vulgaris in Sanglah General Hospital Denpasar. This study aimed to determine the correlation between H<sub>2</sub>O<sub>2</sub> and catalase serum level to the risk of acne vulgaris.

## MATERIALS AND METHODS

This study is an observational analytical study using the case-control design. This study was conducted in the Dermatology and Venereology Outpatient Clinic of Sanglah General Hospital Denpasar on the period of October 2017 to November 2017. Diagnosis of acne vulgaris was made by a physical examination in the outpatient clinic, while plasma H<sub>2</sub>O<sub>2</sub> and catalase levels measurements were done in Universitas Udayana Analytical Laboratory Unit.

Study samples were collected from the reachable population using consecutive sampling design, which was taken from patients that went to Dermatovenereology Outpatient Clinic of Sanglah General Hospital Denpasar. Patients diagnosed with acne vulgaris and fulfilled both inclusion and exclusion criteria are used as cases. Each case

was paired with one control which fulfilled both inclusion and exclusion criteria then matched by age and sex. Patients with acne vulgaris, had the range of age between 12 to 55 years old, could be both male or female, and were willingly agreed to take part on the study confirmed by signing an informed consent were put on case group; meanwhile, patients without acne vulgaris were put on the control group. Patients with a history of smoking, alcohol consumption, tuberculosis infection, cardiovascular diseases, diabetes mellitus, asthma, atopic, malignancy, chronic inflammation such as melasma and atopic dermatitis, pregnant women, consuming antioxidants, and using acne vulgaris treatment during the period of the study were excluded from the study. Data collected were then checked, coded, processed, then both descriptively and analytically analysed using SPSS version 16.

## RESULTS

Subjects that fulfilled both inclusion and exclusion criteria had a total of 76 individuals, grouped into 38 subjects with the inflammatory type of acne vulgaris as case group and 38 subjects without acne vulgaris as the control group, matched by age and sex. Basic characteristics of research samples based on descriptive analysis are listed in Table 1.

Shapiro-Wilk test ( $p > 0.05$ ) was used to see the normality of plasma H<sub>2</sub>O<sub>2</sub> and catalase levels on both case and control groups. Results of the normality test can be seen in Table 2.

Wilcoxon test was used to compare subject characteristics based on H<sub>2</sub>O<sub>2</sub> level of both case and control groups with the result of  $p < 0.001$ . On the other hand, Paired t-test was used to compare subject characteristics based on catalase level of both case and control groups with the results of  $p < 0.001$ . Levene test was used to see the homogeneity. Results can be seen in Table 3.

Receiver operating characteristic (ROC) curve was used to determine the standard cut off point of plasma H<sub>2</sub>O<sub>2</sub> level with the result of 0.62  $\mu\text{mol/mL}$ . This means that plasma H<sub>2</sub>O<sub>2</sub> levels were considered high if it was  $> 0,62 \mu\text{mol/mL}$  and were considered normal if  $\leq 0,62 \mu\text{mol/mL}$ . Fisher test was then used, with the results listed in Table 4.

Odds ratio on this population was 13.67 (95%CI: 4.59-40.62;  $p < 0.001$ ). This means that patients with high plasma H<sub>2</sub>O<sub>2</sub> levels were 13.67 times more likely to develop acne vulgaris compared to patients with normal H<sub>2</sub>O<sub>2</sub> levels.

ROC curve was used again to determine the standard cut off point of plasma catalase level with the result of 0.58 U/ml. This means that plasma catalase levels were considered low if it was  $< 0.58 \text{ U/ml}$  and were considered normal if it was  $\geq 0,58 \text{ U/ml}$

**Table 1** Case and control subject characteristics

Characteristics	Group	
	Case n=38 (%)	Control n=38 (%)
Age		
12-16 years old	3 (7.9)	0 (0)
17-25 years old	20 (52.6)	24 (63.2)
26-35 years old	13 (34.2)	12 (31.6)
36-45 years old	2 (5.3)	2 (5.3)
46-55 years old	0 (0)	0 (0)
Mean $\pm$ SD	23.95 $\pm$ 6.65	24.29 $\pm$ 6.05
Sex		
Male	13 (34.2)	13 (34.2)
Female	25 (65.8)	25 (65.8)
Acne lesion clinical manifestation		
Non-inflammatory acne	23 (60.5)	N/A
Inflammatory acne	15 (39.5)	
H <sub>2</sub> O <sub>2</sub> ( $\mu\text{mol/ml}$ )		
Mean $\pm$ SD	0.68 $\pm$ 0.03	0.42 $\pm$ 0.04
Catalase (U/ml)		
Mean $\pm$ SD	0.48 $\pm$ 0.06	0.74 $\pm$ 0.07

SD: standard deviation

**Table 2** Normality test of plasma H<sub>2</sub>O<sub>2</sub> and catalase levels

Variable	p-value
H <sub>2</sub> O <sub>2</sub>	0.001
Catalase	0.34*

\*normal distribution (p>0.05)

**Table 3** Homogeneity test of plasma H<sub>2</sub>O<sub>2</sub> and catalase levels

Variable	p-value
H <sub>2</sub> O <sub>2</sub>	0.35*
Catalase	0.04

\*data variants are homogeneous (p>0.05)

**Table 4** High Plasma H<sub>2</sub>O<sub>2</sub> Levels as a Risk Factor for Acne Vulgaris

Variable	Group		Odds ratio	95% CI	p-value
	Case n=38 (%)	Control n=38 (%)			
Elevated H <sub>2</sub> O <sub>2</sub> (> 0.62 µmol/ml)	35 (92.1)	0 (0)	13.67	4.59-40.62	<0.001*
Normal H <sub>2</sub> O <sub>2</sub> (≤ 0.62 µmol/ml)	3 (7.9)	38 (100)			

\*p-value is significant if < 0.05

**Table 5** Low plasma catalase level as a risk factor for acne vulgaris

Variable	Group		Odds ratio	95% CI	p-value
	Case n=38 (%)	Control n=38 (%)			
Low catalase (< 0.58 U/ml)	36 (94.7)	0 (0)	20.00	5.18-77.21	<0.001*
Normal catalase (≥ 0.58 U/ml)	2 (5.3)	38 (100)			

\*p-value is significant if <0.05

ml. Fisher test was then used again, with the results listed in Table 5.

Odds ratio on this population was 20.00 (95%CI: 5.18-77.21; p < 0.001). This means that patients with low catalase levels were 20.00 times more likely to develop acne vulgaris compared to patients with normal catalase levels.

## DISCUSSION

Based on age category, this study showed that acne vulgaris was more likely to develop on the age group of 17-25 years old for as many as 20 individuals (52.6%) with none found on the age group of 46-55 years old, as shown on Table 1. A retrospective study conducted by Ayudianti (2014) in Dr. Soetomo Regional General Hospital Surabaya

from 2008 to 2010 shared the same result in which the age group of 15-24 years old account for 64.3% cases with the least found in the age group of ≥ 45 years old with only 0.8% cases.<sup>12</sup> Another research by Mizwar *et al.* (2013) in Dermatovenerology Outpatient Clinic of Prof. dr. R.D. Kandou General Hospital Manado from 2008 to 2010 showed that acne was most commonly found in the age group of 15-24 years old, in the total of 76 patients (62.8%) and least found in the age group of ≥45 years old with only five patients (4.1%).<sup>13</sup> Androgen hormones are excessively released in new-borns, resulting in sebum overproduction. Androgen production will then undergo regression in later childhood leading to decrease of sebum production. Adrenal and gonad glands will then produce more androgen which promote enlargement of sebaceous glands followed by sebum secretion in puberty.<sup>14</sup> Dehydroepiandrosterone sulphate (DHEAS) hormone will lower on adulthood and continue to reside for a lifetime. The decrease of DHEAS hormone precedes the decrease of sebum production. This explains why acne is less commonly found in older age groups.<sup>15</sup>

Acne vulgaris frequency was found higher in women who accounted for 25 patients (65.8%) in this study. A study by Ayudianti also showed that acne was more frequently found in women compared to men.<sup>12</sup> Another study by Mizwar also showed that acne frequency was dominated by women with as much as 75 patients (61.9%).<sup>13</sup> The dominance of women may be related to hormonal factors of the menstrual cycle. Cosmetic use may also contribute to the abovementioned statement.<sup>16</sup> Also, women had higher awareness and attention levels towards outer appearance compared to men, resulting in being more aware of seeking for treatment.<sup>12</sup>

This study showed that plasma H<sub>2</sub>O<sub>2</sub> mean levels were significantly higher on the case group (0.68 ± 0.03 µmol/mL) compared to the control group (0.42 ± 0.04 µmol/mL). A study by Akamatsu *et al.* showed that there was a significant increase in plasma H<sub>2</sub>O<sub>2</sub> levels in inflammatory acne case group compared to comedonal acne and control groups.<sup>17</sup> Studies on the field of plasma H<sub>2</sub>O<sub>2</sub> in acne subjects remain insufficient. Odds ratio found on this study was 13.67, which means patients with high plasma H<sub>2</sub>O<sub>2</sub> had 13.67 times increased risk of developing inflammatory acne compared to patients with normal plasma H<sub>2</sub>O<sub>2</sub> levels (95%CI: 4.59-40.62; p < 0.001). A study conducted by Akamatsu *et al.* also showed that plasma H<sub>2</sub>O<sub>2</sub> mean levels were significantly higher on inflammatory acne compared to comedonal acne and control patients.<sup>17</sup> These statements gave stronger evidence

of the oxidative stress role of inflammatory acne pathogenesis by the elevation of  $H_2O_2$  oxidant levels.

This study showed that plasma catalase mean levels of case group were significantly lower ( $0.48 \pm 0.06$  U/mL) compared to the control group ( $0.74 \pm 0.07$  U/mL). The results of the study conducted by Arican *et al.* supported this statement, in which catalase activity was significantly lower on acne patients ( $8.5 \pm 1.22$  U/g Hb) compared to the control group ( $13.8 \pm 2.31$  U/g Hb).<sup>11</sup> Another study conducted by Sarici *et al.* showed that catalase activity was significantly lower on patients with acne vulgaris ( $41.2 \pm 12.7$  U/mg) compared to patients without acne vulgaris ( $52.4 \pm 18.5$  U/mg).<sup>7</sup> Also, a study by Al-Shobaili showed that catalase antioxidant enzyme activities on the case group were lower ( $0.4 \pm 0.2$  U/mL) compared to the control group ( $0.6 \pm 0.1$  U/mL).<sup>7</sup> Odds ratio was found with 20.00, which means that patients with lower catalase had 20.00 times increased risk of developing inflammatory acne compared to patients with normal catalase levels (95%CI: 5.18-77.21;  $p < 0.001$ ). With these findings, the author suggested that another experimental study is necessary to comprehend more of catalase therapy effectivity on acne vulgaris.

## CONCLUSION

High plasma  $H_2O_2$  levels and low plasma catalase levels are risk factors of acne vulgaris.

## CONFLICT OF INTEREST

Authors stated no conflict of interest regarding this article.

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## AUTHOR CONTRIBUTIONS

All authors contributed to this study

## ETHICAL CLEARANCE

This research has been granted ethical clearance by the Research Ethics Committee of Medical Faculty of Universitas Udayana/Sanglah General Hospital, Denpasar with the registration code of 2224/UN.14.2/KEP/2017.

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