



Coenzyme Q10 Supplementation as an Adjuvant Therapy Potentially Increase Serum Superoxide Dismutase Levels in Acne Vulgaris Patients

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Abstract

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BACKGROUND: Acne vulgaris (AV) is a chronic inflammatory disease in the pilosebaceous unit. Recent research has begun to focus on the essential relationship between oxidative stress and the pathogenesis of AV. The use of antioxidants like coenzyme Q10 (CoQ10) that has various advantages as adjuvant therapy is expected to be beneficial for AV.

AIM: The study was aimed to analyze the effect of CoQ10 supplementation on serum SOD levels and the severity of AV patients.

METHODS: A double blind-randomized controlled trial was carried out on 36 patients with AV and classified according to severity degree of AV. These patients were randomly divided into two groups (treatment group with tretinoin 0.025% cream and once-daily supplementation of CoQ10 100 mg tablet; and placebo group with tretinoin 0.025% cream and once-daily placebo tablet). Response to treatment was based on serum superoxide dismutase (SOD) level and AV severity degree.

RESULTS: Administration of CoQ10 to AV patients significantly increase serum SOD level ($p = 0.008$) and improves the severity of AV after 8 weeks ($p = 0.008$).

CONCLUSION: CoQ10 supplementation can increase serum SOD levels and improve the severity of AV.

Introduction

Acne vulgaris (AV) is a chronic inflammatory disease in the pilosebaceous unit and is more common in adolescents but can continue into adulthood [1], [2], [3]. Based on the Indonesian Dermatology Study Group in 2013, AV ranks 3rd most of the number of visitors to the Department of Dermatovenereology Hospitals and Clinics in Indonesia [4]. Pathogenesis of AV involves four main components, as well as excessive sebum production, abnormal keratinization of the follicle, inflammation, and bacterial colonization of *Propionibacterium acnes* (*P. acnes*) [1], [2], [3]. Recent research has begun to focus on the essential relationship between oxidative stress and pathogenesis of AV through the formation of reactive oxygen species (ROS) and lipid peroxide, where several mechanisms and molecular pathways occur, namely activation of toll-like receptors (TLRs), peroxisome proliferator-activated receptors, natural immune system, and mechanistic target of rapamycin pathways [5], [6], [7], [8].

The skin has developed a complex and specific endogenous anti-oxidative mechanism to overcome problems that arise due to ROS through enzymatic antioxidants, namely superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), which play a role in neutralizing ROS and preventing oxidative damage to cells and tissues [9], [10], [11]. SOD is an important enzymatic antioxidant that acts as the first line of defense and is considered a key antioxidant. SOD scavenges free radical anion superoxide (O_2^-) and reduces their toxicity. SOD converts highly reactive O_2^- to hydrogen peroxide, which by de-mutating O_2^- , SOD prevents the release of iron ions and the formation of harmful ROS such as hydroxyl radicals (OH^\cdot). SOD also protects vascular nitric oxide (NO) signaling by preventing its reaction with O_2^- and preventing the formation of peroxynitrite, which is a dangerous reactive nitrogen species [3], [12].

The classification of AV severity in Indonesia uses the Lehmann grading system recommended by the Indonesian Acne Expert Meeting in 2015 based on mild, moderate, and severe by calculating the total amount from comedones, papules/pustules, and

nodules/cysts [13]. Topical tretinoin is the first choice as a standard therapy of AV [14]. Considering the important role of oxidative stress in the pathogenesis of AV, the use of antioxidants as adjuvant therapy is beneficial for AV [7], [15], [16]. Adjuvant therapy is a treatment that is given together with the main therapy to accelerate healing or improve skin conditions during treatment [13], [14]. The concept of antioxidant therapy aims to strengthen the endogenous antioxidant defenses against oxidative stress more effectively [13], [17], [18].

Coenzyme Q10 (CoQ10) or ubiquinone is a liposoluble compound which is a non-enzymatic endogenous antioxidant that works as the most essential cofactor and has various advantages such as its activity in producing cellular energy, increasing the work capacity of enzymatic antioxidants in taking free radicals, having anti-inflammation through antioxidant activity, inhibits the initiation and propagation phase of lipid peroxide, and regenerates other antioxidants such as tocopherol and ascorbate [18], [19], [20], [21], [22], [23]. The recommended systemic dose of CoQ10 is 30–90 mg/day, where clinical effects take up to 8 weeks [24], [25], [26]. So far, there has never been a research article that discusses the effect of oral CoQ10 supplementation on SOD levels in AV patients. Therefore, this research to study the effect of CoQ10 on serum SOD levels in AV patients.

Methods

Research design

This study was carried out for a period from December 2019 to February 2020. Thirty-six women clinically diagnosed with AV, who attended the outpatient Department of Dermatology and Venereology, Dr. Kariadi Hospital, were enrolled in this study. Before initiation of the study, each subject was informed about the aim of the study and signed informed consent. Ethical approval for this study was obtained from (376/EC/KEPK-RSDK/2019). The inclusion criteria were: Mild to moderate-severe AV patients, female, age 20–40 years, normal body mass index, mild to normal stress level (assessed by Beck's Depressed Inventory); not taking drugs (antibiotics, anti-inflammatory, beta-blocker antihypertensive, statin antihyperlipidemic, warfarin, other vitamins, and antioxidants) in the past 1 month; not pregnant and breastfeeding; not smoking, and are willing to take part in this study to completion, while exclusion criteria include: Patients whose blood samples cannot be collected (due to technical problems) and patients who suddenly refused while taken the blood sample.

The study was performed with 36 patients randomly allocated into two groups.

$$N1 = n2 = 2 \left(\frac{(1.96 + 0.84) \times 0.508}{(11.234 - 10.726)} \right)^2 = 16$$

The minimum sample required is calculated as 16, to anticipate a non-response or drop-out percentage as 10%, $16 + (10\% \times 16) = 17.6$. Then final sample = 18 samples for this study.

The first group consists of 18 patients, treated with tretinoin 0.025% cream and CoQ10 100 mg tablet/day orally; the second group consists of 18 patients, treated with tretinoin 0.025% cream and placebo tablet/day orally. The use of sunscreen cream of SPF 30 was suggested during the study period. The diagnosis of AV was based on the total lesion count of comedones, papules, pustule nodules, and cysts according to the Lehmann grading system of AV severity degree. The duration required for each patient to complete the course of the treatment was 8 weeks, clinical and laboratory assessment would be carried out at baseline and by the end of this period. Side effects would be looked for by asking the patients about any abnormal effect that appeared throughout the whole course of treatment.

Sample analysis

Blood samples for SOD3 analysis were collected between December 2019 and February 2020. Blood samples were collected 3 ml from venipuncture allow samples to clot for 2 h at room temperature or overnight at 4°C before centrifuge for 15 min at $1000 \times g$ at 2–8°C. SOD3 serum was examined with enzyme-linked immunosorbent assay (ELISA) Elabscience®.

Statistical analysis

The data obtained were processed with the Statistical Package for Social Science program for Windows. Paired t-test, Wilcoxon, Mann–Whitney, McNemar, and Chi-square would be used to compare between the different groups' concerning and post-treatment values $p \leq 0.05$ is considered as a significant change. Spearman correlation test would be used to compare between SOD serum level and severity of AV. The degree of relationship is expressed by the magnitude of the correlation coefficient. The intention to treat analysis was used in this study

Results

This study involved 36 research subjects divided into 2 groups: The treatment group with CoQ10

(n = 18 subjects) and the control group with placebo (n = 18 subjects). The number of research subjects at the end of the study is the same as at the beginning of the study, no research subjects were found to experience drop-outs, as shown in Figure 1.

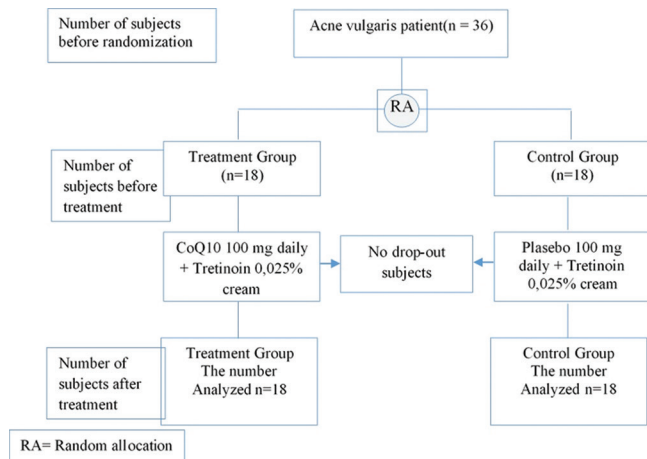


Figure 1: Diagram of the number of subjects in the treatment and control group in the study of the effect of coenzyme Q10 on superoxide dismutase serum levels and severity of acne vulgaris at Dr. Kariadi General Hospital Medical Center in December 2019–February 2020 (n = 36)

Table 1 shows that the mean age of the study subjects in the treatment group was 25.9 ± 4.52 years with the youngest age being 21 years and the oldest was 33 years. The mean age of the study subjects in the control group was older than the treatment group which was 26.5 ± 5.82 years with the youngest age being 20 years and the oldest was 40 years. Statistical test results showed that the mean age difference of the study subjects between the treatment group and the control group was not significant ($p = 0.9$; Mann–Whitney test). The type of occupations of the research subjects in the treatment group was students (44.4%), while in the control group, the majority were office employees (33.3%). Statistical test results showed that this difference was not significant ($p = 0.1$; Fisher’s exact test). In the treatment group that most of the study subjects had no sun exposure (55.6%), whereas, in the control group, the number of subjects without sun exposure was as much as subjects with sun exposure (each 50%). Statistical test results showed

Table 1: Characteristics of study subjects in the research group effect of CoQ10 on SOD serum levels and severity of AV at Dr. Kariadi General Hospital Medical Center Semarang in December 2019–February 2020 (n = 36)

Characteristics	Group		p
	Treatment (n = 18)	Control (n = 18)	
Age; mean \pm SD; median (min–max)	25.9 \pm 4.52; 25 (21–33)	26.5 \pm 5.82; 25 (20–40)	0.9*
Type of occupations; n (%)			0.1 [§]
Doctor	7 (38.9)	4 (22.2)	
University student	8 (44.4)	5 (27.8)	
Office employee	1 (5.6)	6 (33.3)	
Midwife. nurse	2 (11.1)	1 (5.6)	
Housewife	0 (0.0)	2 (11.1)	
Sun exposure			0.7
None	10 (55.6)	9 (50.0)	
Exist	8 (44.4)	9 (50.0)	

(*): Mann–Whitney test. (§): Fisher’s exact test, χ^2 test, SOD: Superoxide dismutase, AV: Acne vulgaris, CoQ10: Coenzyme Q10.

that the difference in the distribution of sun exposure between the treatment and control groups was not significant ($p = 0.7$; χ^2 test).

Figure 2 shows that in the treatment group, there was a significant increase in serum SOD levels from before to after treatment ($p < 0.001$; Wilcoxon test), whereas in the control group, there was only a small increase that was not significant ($p = 0.7$).

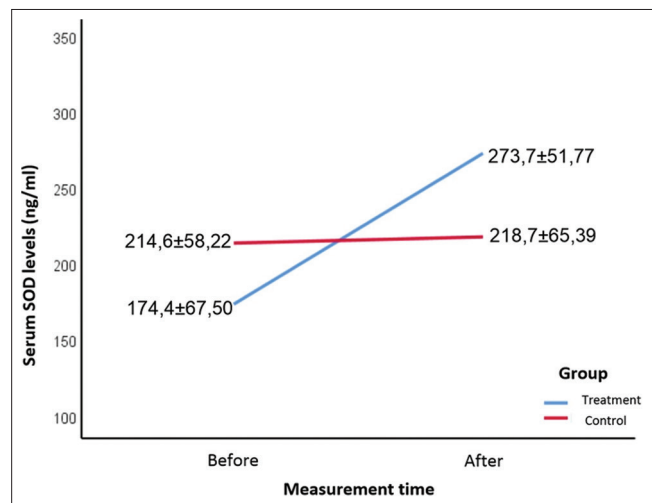


Figure 2: Changes in serum SOD levels from before to after treatment in the study of the effect of coenzyme Q10 on superoxide dismutase serum levels and severity of acne vulgaris at Dr. Kariadi General Hospital Medical Center Semarang in December 2019–February 2020 (n = 36)

Table 2 shows that the serum SOD levels before treatment in the treatment group which was 174.4 ± 67.50 ng/ml were lower than the control group, which was 214.6 ± 58.22 ng/ml, but statistically, the difference was not significant ($p = 0.06$; unpaired t-test). Serum SOD levels after treatment in the treatment group that was 273.7 ± 51.77 ng/ml were significantly higher than the control group, which was 218.7 ± 65.39 ng/ml ($p = 0.008$; unpaired t-test). Delta SOD serum treatment group that is 99.3 ± 63.65 ng/ml was significantly higher than the control group, which was 4.1 ± 54.00 ng/ml ($p < 0.001$; unpaired t-test).

Table 2: Serum SOD levels in the treatment and control groups in the study of the effect of CoQ10 on SOD serum levels and severity of AV at Dr. Kariadi General Hospital Medical Center Semarang in December 2019–February 2020 (n = 36)

Measurement time	Serum SOD levels (ng/ml) in group:		p*
	Treatment (n = 18)	Control (n = 18)	
	Mean \pm SD; Median (Min–Max)	Mean \pm SD; Median (Min–Max)	
Before	174.4 \pm 67.5; 167.4 (81.5–315.8)	214.6 \pm 58.22; 196.2 (147.7–346.8)	0.06
After	273.7 \pm 51.77; 270.9 (147.8–364.8)	218.7 \pm 65.39; 212.9 (116.5–355.6)	0.008
Delta	99.3 \pm 63.65; 76.1 (13.4–235.2)	4.1 \pm 54.00; 14.0 (–118.2–77.7)	<0.001
p** before versus after	<0.001	0.7	

Delta: Serum superoxide dismutase levels after - serum superoxide dismutase levels before (*) Unpaired t-test, (**) Paired t-test, SOD: Superoxide dismutase, AV: Acne vulgaris, CoQ10: Coenzyme Q10.

Table 3 shows the severity of AV based on the Lehmann grading system in the treatment and control groups. Statistical test results showed that the change in the severity of AV in the treatment

Table 3: Severity degree of AV in the study group in the study of the effect of CoQ10 on SOD serum levels and severity of AV at Dr. Kariadi General Hospital Medical Center Semarang in December 2019–February 2020 (n = 36)

Severity degree of AV	Group (%)		P
	Treatment (n = 18)	Control (n = 18)	
Before/pre-treatment			
Mild	6 (33.3)	6 (33.3)	1.0
Moderate	6 (33.3)	6 (33.3)	
Severe	6 (33.3)	6 (33.3)	
After/post-treatment			
Mild	14 (77.8)	10 (55.6)	0.3 ^s
Moderate	4 (22.2)	7 (38.9)	
Sever	0 (0.0)	1 (5.6)	

p = 0.008, p = 0.05, (S): Fisher's exact test, χ^2 test, treatment group before and after: p = 0.008, McNemar's test, control group before and after: p = 0.05, McNemar's test, SOD: Superoxide dismutase, AV: Acne vulgaris, CoQ10: Coenzyme Q10.

group was significant ($p = 0.008$; McNemar's test), while the change in the severity of AV in the control group was not significant ($p = 0.05$; McNemar's test). The distribution of the severity of AV before treatment between the treatment groups was the same as the control group ($p = 1.01$ χ^2 test). After treatment in both the treatment and control groups, the most was a mild degree of AV, the next was moderate, and there was only 1 subject with every degree of AV in the control group. Statistical test results showed that the difference in the distribution of the severity of AV after treatment between the treatment and control groups was not significant ($p = 0.3$; Fisher's exact test).

Table 4 shows that the mean serum SOD levels before the lowest treatment was in the group with severe severity of AV which was 181.9 ± 65.56 ng/ml, while the highest was in the mild AV group which was 212.3 ± 71 , 96 ng/ml. Statistical test results showed that differences in serum SOD levels based on AV degrees before treatment were not significant ($p = 0.5$; one-way ANOVA test). The highest serum SOD level after treatment was in the group with mild AV severity that was 260.2 ± 63.2 ng/ml and the lowest was in the group with severe AV severity that was 209.8 ± 0.00 ng/ml. Statistical test results also showed differences in serum SOD levels based on the severity of AV when after test was not significant ($p = 0.06$; one-way ANOVA test).

Table 4: Serum SOD levels based on the severity of AV before and after treatment in the study of the effect of CoQ10 on SOD serum levels and severity of AV at Dr. Kariadi General Hospital Medical Center Semarang in December 2019–February 2020 (n = 36)

Severity degree of AV	Serum SOD levels (ng/ml) Mean \pm standard deviation; Median (Min-Max)
Before treatment	
Mild (n = 12)	212.3 \pm 71.96; 228.2 (87.8–302.4)
Moderate (n = 12)	189.2 \pm 59.80; 175.6 (83.0–315.80)
Severe (n = 12)	181.9 \pm 65.56; 172.7 (81.5–346.80)
After treatment	
Mild (n = 24)	260.2 \pm 63.2; 268.3 (116.5–364.8)
Moderate (n = 11)	218.9 \pm 62.85; 222.7 (125.7–338.5)
Severe (n = 1)	209.8 \pm 0.00; 209.8 (209.8–209.8)

One-way ANOVA test: Before treatment $p = 0.5$, After treatment $p = 0.06$, SOD: Superoxide dismutase, AV: Acne vulgaris, CoQ10: Coenzyme Q10.

Table 5 shows that the highest delta SOD was 235.21 ng/ml. It was found in the subjects of the

treatment group with a mild degree of severity before and after treatment. The lowest delta SOD was -118.17 ng/ml which was found in the subjects of the treatment group with a severe severity before treatment and a moderate severity after treatment.

Table 5: Delta data of serum SOD levels in each study subject based on the severity of AV and the research group in the study of the effect of CoQ10 on SOD levels and serum AV severity at Dr. Kariadi General Hospital Medical Center Semarang in December 2019–February 2020 (n = 36)

Severity degree of AV		Group	Delta serum SOD levels (ng/ml)
Before treatment	After treatment		
Mild	Mild	Treatment	235.21
Mild	Mild	Treatment	-40.41
Mild	Mild	Control	164.7
Mild	Mild	Control	9.26
Mild	Mild	Treatment	19.36
Mild	Mild	Treatment	29.94
Mild	Mild	Treatment	-82.44
Mild	Mild	Control	130.05
Mild	Mild	Treatment	76.81
Mild	Mild	Control	34.64
Mild	Mild	Control	48.99
Mild	Mild	Control	13.44
Moderate	Mild	Control	-31.23
Moderate	Mild	Control	34.83
Moderate	Mild	Control	15.26
Moderate	Moderate	Treatment	9.31
Moderate	Mild	Treatment	162.44
Moderate	Moderate	Control	22.65
Moderate	Mild	Control	67.79
Moderate	Mild	Treatment	92.93
Moderate	Moderate	Control	12.68
Moderate	Moderate	Treatment	74.4
Moderate	Moderate	Control	-55.23
Moderate	Mild	Control	156.74
Severe	Mild	Treatment	77.73
Severe	Moderate	Treatment	71.9
Severe	Mild	Treatment	200.29
Severe	Moderate	Treatment	118.15
Severe	Moderate	Control	40.29
Severe	Moderate	Treatment	77.7
Severe	Mild	Control	-30.98
Severe	Moderate	Treatment	66.93
Severe	Mild	Control	66.29
Severe	Mild	Control	64.46
Severe	Moderate	Treatment	-118.17
Severe	Severe	Treatment	24.19

SOD: Superoxide dismutase, AV: Acne vulgaris, CoQ10: Coenzyme Q10.

Table 6 shows a significant correlation between serum SOD levels after treatment with the severity of AV after treatment ($p = 0.04$; Spearman's correlation test). The analysis also shows the relationship between serum SOD levels before and delta serum SOD levels with a degree of AV severity are not significant.

Table 6: Relationship between the severity of AV with serum SOD levels and delta in the study of the effect of CoQ10 on the level of SOD serum and severity of AV at Dr. Kariadi General Hospital Medical Center Semarang in December 2019–February 2020 (n = 36)

Severity degree of AV and serum SOD levels	Severity degree of AV before treatment	Severity degree of AV after treatment	Serum SOD levels before treatment	Serum SOD levels after treatment	Delta serum SOD levels
Severity degree of AV before treatment	1.0	0.51 ($p = 0.001$)	-0.25 ($p = 0.1$)	-0.11 ($p = 0.5$)	0.11 ($p = 0.5$)
Severity degree of AV after treatment	–	1.0	-0.11 ($p = 0.52$)	-0.33 ($p = 0.04$)	-0.16 ($p = 0.3$)
Serum SOD levels before treatment	–	–	1.0	0.33 ($p = 0.04$)	0.11 ($p = 0.5$)
Serum SOD levels after treatment	–	–	–	1.0	-0.53 ($p = 0.001$)

Spearman's correlation test, SOD: Superoxide dismutase, AV: Acne vulgaris, CoQ10: Coenzyme Q10.

Discussion

This study was a randomized controlled clinical trial, in which subjects in mild, moderate, and severe AV patients have treated with CoQ10 supplementation 1 mg × 100 mg in the treatment group and placebo 1 mg × 100 mg for 8 weeks in the control group. Researchers used the pre-test and post-test design and double-blind method. Based on the data of the characteristics of the research subjects, all subjects in the treatment and control group were women (100%), according to a study shows that two-thirds of patients who go to a dermatologist with AV complaints are women [27]. All subjects were in the normalized weight category (100%) and examination with the Beck's Depression Inventory questionnaire, none of the subjects experienced depression (100%) and obtained that there are differences in age, type of occupations, and exposure to sunlight. The absence of significant differences in the characteristics of research subjects between the treatment and control groups shows that the potential variable characteristics as confounding variables can be controlled.

Serum SOD levels after treatment in the treatment group were significantly higher than in the control group ($p = 0.008$; unpaired t-test), whereas the delta serum SOD treatment group was significantly higher than the control group ($p < 0.001$; unpaired t-test). It can be concluded that there is an improvement in serum SOD levels in the treatment group compared to the control group, this is because CoQ10 supplementation can increase the enzymatic endogenous antioxidant activity which is the first-line defense system, namely SOD [2], [3]. A meta-analysis is of 13 clinical randomized controlled trials of 912 potential citations found to be eligible by Jorat *et al.* [28] showed that CoQ10 supplementation significantly increased SOD levels as a marker of inflammation and oxidative stress in coronary arterial disease patients compared control group, where it has been previously stated that there is a relationship between oxidative stress and pathogenesis of AV [4]. Research conducted by Zhang *et al.* [29] also found that the use of CoQ10 significantly reduces the production of UV-induced ROS as a marker of oxidative stress.

The severity of AV in this study found a clinical improvement in decreasing the severity of AV where most AV sufferers were in mild degrees and no more severe AV degrees were found after therapy in the treatment group. There was also a clinical improvement in the severity of AV in the control group, whereas most AV sufferers were in mild degrees, but patients with severe AV were still found, although the results were not significant ($p = 0.05$; McNemar's test). Research subjects with mild degrees in the treatment and control groups, although still in a mild degree, decreased in the number of non-inflammatory and inflammatory

lesions following the Lehmann grading system. This shows that there is a clinical improvement in the degree of AV greater in the treatment group compared to the control group. Several new studies have shown that AV sufferers may experience increased oxidative stress and have decreased levels of endogenous antioxidants in the blood. This results in higher levels of ROS produced by neutrophils, wherein ROS participates in the development of inflammatory AV. Therefore, it is mentioned that antioxidant supplements may be a valuable adjuvant in AV [30]. CoQ10 therapy as an antioxidant can reduce the production of free radicals by increasing the activity of endogenous antioxidants, regenerating Vitamin E, reducing DNA damage and oxidative damage in the mitochondria [31]. Differences in severity distribution AV after treatment between the treatment and control groups were not significant, this could be due to all subjects being given a topical retinoid, that is, tretinoin 0.025%, which had a role in AV therapy. Tretinoin works to normalize desquamation by reducing the proliferation of keratinocytes and blocking several important inflammatory pathways in AV, namely TLR's, leukocyte migration, and the AP-1 pathway, which by suppressing TLR's expression can reduce the release of inflammatory cytokines and NO, also inhibit inflammation. Randomized controlled trials have proven that topical tretinoin as monotherapy significantly reduces inflammatory lesions comparable to those in non-inflammatory lesions. Research conducted by Leyden *et al.* in 2017 states that there was a significant clinical improvement in inflammatory AV and decreased severity of AV after monotherapy with topical tretinoin for 12–15 weeks [32].

This study shows that there is no significant correlation between serum SOD levels before treatment with AV severity, but there is a significant correlation between serum SOD levels after treatment with AV severity. The mean serum SOD level before treatment was the lowest in the severe AV group, which was 181.9 ± 65.56 ng/ml, while the highest was in the mild AV group which was 212.3 ± 71.96 ng/ml. Serum SOD levels after the highest treatment were in the mild AV group, which was 260.2 ± 63.2 ng/ml and the lowest was in the severe AV group, which was 209.8 ± 0.00 ng/ml. Research conducted by Perihan *et al.* states that SOD levels are decreased in patients with severe AV compared with mild and moderate AV ($p < 0.05$), however, the correlation between serum SOD levels and the severity of AV is not significant. This can be due to an increase in antioxidant enzymes in inflammation as in AV, possibly inducing subunits of each oxidative biomarker, but the occurrence of severe inflammation can also cause decreased antioxidant enzyme activity [33]. Other research conducted by Al-Shobaili *et al.* [34], in as many as 50 serum samples of subjects with AV, showed that SOD decreased significantly with the increase in severity of AV. Decreased serum SOD levels indicate that in AV, there is a disturbance in the antioxidant balance which causes an increase in ROS

levels, thus contributing to an increase in oxidative stress. Besides, this finding also shows that oxidative stress increases in AV along with an increase in the severity of the disease.

Conclusion

CoQ10 supplementation as adjuvant therapy for AV can increase serum SOD levels and improve the severity of AV compared with placebo supplementation. Future studies are necessary to the understanding of the relationships between SOD and other antioxidant enzymes such as GSH-Px, CAT, malondialdehyde as indicators of oxidative stress, air pollution, and pro-inflammatory factors may improve our ability to develop interventions aimed to decrease oxidative stress

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