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ORIGINAL ARTICLE

Relationship of whole blood zinc levels to acne severity among Filipinos 18-25 years old: a cross-sectional comparative study in a tertiary government hospital

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ABSTRACT

INTRODUCTION Acne Vulgaris is one of the most common dermatologic diagnoses in the world. It can persist for years, result in permanent scarring, and have serious adverse effects on psychosocial development.

OBJECTIVES This study aims to determine the relationship between whole blood zinc levels and severity of acne.

METHODS This is a cross-sectional comparative study. Whole blood zinc levels of 30 patients with acne vulgaris divided into mild (n=10), moderate (n=10), and severe (n=10), and 10 healthy patients were measured. Acne severity was evaluated using the Global Acne Grading System (GAGS).

RESULTS A total of 40 patients participated in this study. The mean whole blood zinc level in acne patients and non-acne patients were 5.03 ± 1.92 mcg/mL and 7.39 ± 0.79 mcg/mL, respectively. The mean zinc level of the controls was significantly higher compared to that of the acne patients ($p=0.0006$). Furthermore, mean whole blood zinc level of the patients with severe acne was significantly lower compared to that of the controls, mild acne and moderate acne ($p<0.001$). Adjusting for age and sex, there is a significant association between severity of acne vulgaris and blood zinc levels ($p<0.0001$). Specifically, the mean blood zinc level of the patients with moderate and severe acne were significantly lower compared to that of the control group ($p=0.019$ and $p<0.001$, respectively).

CONCLUSION Whole blood zinc levels were inversely correlated with acne vulgaris severity in the Filipino population. Further studies are recommended to determine the role of zinc in the pathogenesis of acne and the effects of oral zinc supplementation on acne patients.

KEYWORDS Acne Vulgaris, Whole Blood Zinc Levels, Global Acne Grading System

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INTRODUCTION

Acne vulgaris is a disorder of the pilosebaceous unit characterized by formation of comedones, papules, pustules, inflamed nodules, and cysts.[1] The four main pathogenic contributors of acne include follicular hyperkeratinization, increased sebum production, *Cutibacterium acnes* (*C. acnes*) within the follicle, and inflammation.[1,2] Most common predilection sites are those with hormone-sensitive sebaceous glands such as the face, neck, chest, upper back, and upper arms.1 Acne vulgaris is the eighth most prevalent disease in the world, affecting 9.4% of the global population.[3] In adults, acne prevalence ranges from 50 to 54% in females and 40 to 42.5% in males.[4,5] This disease is commonly misunderstood to primarily affect teenagers. However, a large proportion of individuals continue to suffer from acne or acquire new-onset acne far after their adolescent years.[4] Up to 64% of individuals have acne persisting into their 20s, and 43% have acne persisting into their 30s.[6] Moreover, the prevalence of acne did not substantially decrease until after the age of 44.[5]

Acne can persist for years and result in disfigurement and permanent scarring. It can cause serious adverse effects on psychosocial development, resulting in emotional problems, withdrawal from society, and depression.[6] Nearly all adolescents experience different severity levels of acne vulgaris, with moderate to severe levels affecting around 20% of this population.[6] In the Philippines, high school students were found to have a mild impairment of quality of life (QOL) due to acne, regardless of severity.[7]

Safe and effective long-term maintenance therapy is necessary to address the chronic and persistent nature of acne.[8] In the last three decades, there has been a significant increase in resistance to antibiotics commonly used to treat acne. This was measured by the increased minimal inhibitory concentration (MIC) against *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) for antibiotics such as erythromycin and tetracycline in patients receiving long-term antibiotic treatment. This increase

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was not observed in patients who did not have antibiotic treatment. *C. acnes* isolates in more recent studies showed resistance to clindamycin, erythromycin, tetracycline, doxycycline, and minocycline.[8-11] This is a significant international public health concern because aside from increase in pathogenic *C. acnes*, resistance can occur in other bacteria more dangerous than *C. acnes*. Given this situation and the complexity of the repercussions of this trend, it is a challenge to maximize the use of non-antimicrobial therapy when treating acne.[8,12-15]

The development of a variety of skin disorders, including acne, has been linked to oxidative status. Oxidative stress may play a major role in the pathogenesis of acne due to the lower plasma levels of the antioxidant enzymes catalase (CAT), superoxide dismutase (SOD), total antioxidant capacity (TAC). Acne patients also had a higher level of malondialdehyde (MDA), a marker for oxidative stress.[16] Zinc is found in all body tissues and is an essential element for normal epithelial differentiation and development. The conformity, stability, and activity of more than 200 metalloenzymes are affected by zinc as well as cell health and proper bodily functions like glandular, reproductive, immune, and neuropsychiatric processes. In skin, it is 5 to 6 times more abundant in the epidermis than in the dermis. Its antioxidant properties have numerous benefits such as protection against ultraviolet rays and oxidative damage by decreasing reactive oxygen species (ROS) and improvement of wound healing and prevention of cancer and cardiovascular diseases.[17,18] At present, there is paucity of data regarding the role of zinc levels in the development or severity of acne vulgaris. Data on favorable effects of dietary factors such as zinc, omega-3 fatty acids, antioxidants, vitamin A, and dietary fiber on acne vulgaris are limited especially in the Philippines.

Zinc deficiency exists both in developed and developing countries. Several factors may affect serum zinc levels. These include low intake of highly absorbable zinc in fresh foods, high phytate content of some staple food, pregnancy, lactation, and increased demands of physiological processes such as growth and sexual maturation.[19] Inductively coupled plasma–atomic emission spectroscopy (ICP-AES) is used for zinc determinations in blood and tissue samples, where the electromagnetic radiation released by free atoms is used to determine the element.[20,21] When whole blood zinc levels were measured from healthy participants in relation to sex and age using atomic absorption spectrophotometry, the mean zinc level obtained in whole human blood from males was 607.0 ± 105.3 micrograms/100 ml and 585.2 ± 122.9 micrograms/100 ml in females. Males had slightly higher zinc levels but the difference was not statistically significant.[22] Zinc deficiency starts when zinc levels reach 66 micrograms/dL for non-pregnant females and 70 micrograms/dL for males older than 9 years old.[23]

A few researches in other countries compared zinc levels in blood with the severity of acne. A study in Iraq measured trace elements in the blood, such as zinc and copper, and correlated it to the severity of acne vulgaris. Patients with severe acne had significantly lower levels of zinc.[24] A study in Iran suggested that zinc levels may be related to the severity and type of acne lesions, with moderate and severe acne patients having lower serum zinc levels than mild acne and control patients.[25] Another study of 173 acne patients showed that retinol binding protein and serum zinc levels were significantly lower in severe acne.[26] The relative decrease of serum zinc levels in acne patients suggests a role for zinc in the pathogenesis of acne vulgaris. Studies about serum or whole blood zinc levels and its association to acne severity in the Philippine setting have not yet been done. Given that acne vulgaris is one of the most common dermatologic diagnoses in the Philippine population and that there is an increase in cases of antibiotic resistance, studies on other treatment modalities for acne vulgaris are timely and significant.

OBJECTIVES

The general objective of this study was to determine the relationship between whole blood zinc levels and the severity of acne vulgaris in Filipino patients 18-25 years old versus normal controls.

The specific objectives were to describe the clinical profile of Filipino patients 18-25 years old with acne vulgaris, to determine the whole blood zinc levels of acne patients compared to controls, and to determine the relationship of the clinical severity of acne vulgaris to whole blood zinc levels.

METHODS

STUDY DESIGN AND SETTING

A cross-sectional comparative study design was utilized for this study which was conducted from November 2017 to March 2018 at the Dermatology outpatient clinic of the East Avenue Medical Center (EAMC). Laboratory services of Hi-Precision Diagnostics were used for measuring whole blood zinc levels.

The study was approved by the ethics review board of EAMC prior to initiation. Informed consent was secured from each participant prior to inclusion in the study. All patients were given proper treatment whether they agreed to participate in the study or not. To ensure confidentiality in data collection, the investigators assigned a code to replace identifiers such as the participant's name.

PARTICIPANTS

The participants of the study included Filipino patients clinically diagnosed with acne vulgaris who are 18 to 25 years old, and normal controls in the same age group. Participants were enrolled from the Dermatology outpatient clinic or Skin Center of EAMC. Participants who were excluded from the study were those who had other chronic dermatoses or systemic disease, took oral supplements or medications within 3 months prior to

joining the study, and those who were pregnant or lactating.

OUTCOME MEASURES

The outcome measures were demographics (age and sex), severity of acne vulgaris based on Global Acne Grading System (GAGS), and whole blood zinc levels.

DATA SOURCES AND MEASUREMENT

Acne severity was assessed using the Global Acne Grading System (GAGS). The GAGS is an acne severity scale that includes six locations on the face, chest, and upper back. A factor is provided for each of the 6 locations based on size (forehead = 2, right cheek = 2, left cheek = 2, nose = 1, chin = 1, chest and upper back = 3). Each of the six areas are graded on a scale of 0-4 based on the most severe lesion present (no lesion = 0, comedones = 1, papules = 2, pustules = 3, nodules = 4). The local score per location is obtained by multiplying the factor with the corresponding score for the most severe lesion. The sum of the local scores from all locations will result to the global score, with zero as the lowest and 44 as the highest possible global score. Acne severity is rated as mild (1-18), moderate (19-30), severe (31-38), and very severe (≥39) with corresponding cut-off global scores.[27]

Twelve milliliters of blood were extracted from each participant with proper aseptic technique. This was properly stored in three EDTA tubes, labelled, refrigerated at 15-25°C, and transported to the laboratory for determination of whole blood zinc levels through ashing acid digestion-inductively coupled plasma (ICP) using Shimadzu ICPS-7510, an inductively coupled plasma emission spectrometer.

SAMPLE SIZE

The program used for the computation of minimum sample size was PASS 2008. Parameters for the computation was obtained from previously published studies. For the one-way ANOVA, a minimum of 40 patients (10 for each acne severity: mild, moderate and severe acne, and 10 for controls) achieved 95% power to detect differences among the means versus the alternative of equal means using an F-test with a significance level of 0.05. The size of the variation in the means was represented by their standard deviation which was 13.30 mg/dL and the common standard deviation within a group was assumed to be 20.00 mg/dL.[24]

STATISTICAL METHODS

All valid data from participants with physical examination and blood test results were included in the analysis. Missing values were not replaced nor estimated during the statistical analysis of outcome variables. Data was encoded in Microsoft Excel and was converted into a Stata file for further data processing and analysis. Stata SE version 12 was used for both descriptive and inferential statistics. Quantitative variables were presented as mean or median while qualitative variables were presented as percentages.

In order to compare the whole blood zinc levels between cases and controls, independent T-test was used. ANOVA was used to compare the whole blood zinc levels by acne severity. Multiple linear regression analysis was performed to determine the association of whole blood zinc levels with acne severity after controlling for the effects of significant confounding variables. All p-values ≤ 0.05 were considered as significant.

RESULTS

CLINICAL PROFILE OF FILIPINO PATIENTS 18-25 YEARS OLD WITH ACNE VULGARIS

A total of 40 patients participated in this study. Among the patients with acne vulgaris, 10 had mild acne, 10 had moderate acne, and 10 had severe acne. The demographic and clinical profile of the patients are shown in Table 1.

The mean age of the patients with acne was 21.63 years with a standard deviation of 2.79 years. The youngest patient in the group was 18 years old while the oldest patient was 25 years old. On the other hand, the mean age of the patients without acne (i.e., controls) was 23.9 years with a standard deviation of 1.2 years. The youngest patient in the group was 22 years old while the oldest patient was 25 years old. 72.5% of the patients in both groups were females. There were 22 (73.30%) female acne patients and 7 (70%) female non-acne patients. The mean GAGS score of the participants with acne was 23.1 with a standard deviation of 10.02. The lowest and highest GAGS scores were 3 and 39, respectively.

WHOLE BLOOD ZINC LEVELS OF ACNE PATIENTS COMPARED TO CONTROLS

The mean blood zinc level of the non-acne patients was 7.39 mcg/mL with a standard deviation of 0.79 mcg/mL. The mean

Table 1. Demographic and clinical characteristics of study participants

Characteristics	Cases (n=30)		Controls (n=10)	
	Mean	S.D.	Mean	S.D.
Age (in years)	21.63	2.79	**23.9**	1.2
GAGS score	23.1	10.02	-	-
	Frequency	Percent	Frequency	Percent
Sex				
Female	22	73.30%	7	70%
Male	8	26.70%	3	30%

Table 2. Mean blood zinc levels (mcg/mL) according to patient group

Group	Mean	95% C.I.	p-value
Controls (n=10)	7.39	6.82, 7.96	0.0006
Cases (n=30)	5.03	4.31, 5.75	

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blood zinc level of the acne patients was 5.03 mcg/mL with a standard deviation of 1.92 mcg/mL. The result of the independent t-test shows that the mean zinc level of the non-acne patients is significantly higher compared to that of the acne patients (p=0.0006) (Table 2).

RELATIONSHIP OF THE CLINICAL SEVERITY OF ACNE VULGARIS TO WHOLE BLOOD ZINC LEVELS

The mean blood zinc level of patients with mild acne was 6.15 mcg/mL with a standard deviation of 1.65 mcg/mL. The mean blood zinc level of patients with moderate acne was 5.83 mcg/mL with a standard deviation of 0.41 mcg/mL. The mean blood zinc level of patients with severe acne was 3.11 mcg/mL with a standard deviation of 1.68 mcg/mL.

The result of the one-way ANOVA shows that the mean blood zinc levels significantly varies by severity of acne vulgaris (p<0.0001) (Table 3). Specifically, using the Bonferroni test, the mean zinc level of the patients with severe acne was significantly lower compared to that of the non-acne patients (p<0.001), patients with mild acne (p<0.001), and patients with moderate acne (p<0.001). Nevertheless, the mean zinc levels of the patients with mild and moderate acne was not significantly different from that of the non-acne patients (p>0.05) (Table 4).

Adjusting for age and sex, there is a significant association between severity of acne vulgaris and blood zinc levels (p<0.0001). Specifically, the mean blood zinc level of the patients with mild acne was 1.11 mcg/mL lower compared to that of the non-acne patients. Nevertheless, it is not statistically significant (p=0.071). On the other hand, the mean blood zinc level of the patients with moderate acne was 1.48 mcg/mL lower compared to that of the control group and it was statistically significant (p=0.019). Lastly, the mean blood zinc level of the patients with severe acne was 4.19 mcg/mL lower compared to that of the control group and it was statistically significant (p<0.001) (Table 5).

Table 3. Mean blood zinc levels (mcg/mL) according to severity of acne vulgaris

Severity of Acne	Mean	95% C.I.	p-value
Controls (n=10)	7.39	6.82, 7.96	**<0.0001**
Mild (n=10)	6.15	4.97, 7.33	
Moderate (n=10)	**5.83**	**5.54, 6.12**	
Severe (n=10)	3.11	1.91, 4.31	

Table 4. Comparison of zinc levels (mcg/mL) by severity of acne vulgaris (Bonferroni test)

Row Mean-Column Mean	Control	Mild	Moderate
Mild	-1.24 0.205		
Moderate	-1.56 0.053	-0.32 1.00	
Severe	-4.28 <0.001	-3.04 <0.001	-2.72 <0.001

Table 5. Association between severity of acne vulgaris and blood zinc levels

Severity of Acne	Coefficient *	95% C.I.	p-value
Controls (n=10)	-	-	-
Mild (n=10)	-1.11	-2.33, 0.1	**0.071**
Moderate (n=10)	-1.48	-2.7, -0.26	0.019
Severe (n=10)	-4.19	-5.43, -2.95	<0.001

*Adjusted for age and sex

DISCUSSION

This cross-sectional comparative study provided the first evidence for the association between whole blood zinc levels and acne vulgaris in the Filipino population. Findings revealed that whole blood zinc levels in patients with severe type of acne vulgaris were significantly lower than that of controls, mild, and moderate acne vulgaris patients. Adjusting for age and sex, the whole blood zinc levels of both severe and moderate types of acne were significantly lower than controls.

A study done by Ozuguz et al showed that serum vitamin E, vitamin A, and zinc were significantly lower in acne vulgaris patients compared to controls. Moreover, patients with severe acne had significantly lower serum vitamin E and zinc levels compared to controls.[28] We had congruent findings in our study regarding the negative correlation of zinc levels and severity of acne vulgaris.

Similarly, Saleh et al showed that the mean value of serum zinc significantly decreased in severe acne compared to normal controls in the Iraqi population.[24] Kaymak et al also found that zinc levels were significantly lower in the acne group when compared to controls.[29] These studies compared acne vulgaris patients with controls without classifying according to severity.

Mogaddam et al found that the mean serum zinc level of acne vulgaris patients was lower compared to those in healthy patients, but it was not statistically significant.[25] This may be due to the participants being mostly classified as having mild acne vulgaris. The participants were composed of 64 mild acne patients, 32 moderate acne patients, and four (4) severe acne patients. Mild acne vugaris may have lower serum zinc levels but are usually not statistically significant when compared to controls.

Rice is a staple food in the Philippines. It is also known to have high phytate content, which may reduce the zinc levels in the blood.[19] This study included non-acne participants in order to be able to limit this possible confounding factor and determine whether the decrease in whole blood zinc levels is related to Filipinos in general or may be associated to acne vulgaris and its severity.

One of the key factors in the pathogenesis of acne vulgaris is inflammation. Oxidative stress is implicated in acne due to the high levels of malondialdehyde activity and low levels of antioxidant enzyme activity.[16] Low zinc levels in acne vulgaris patients may be related to zinc's antioxidant and anti-inflammatory role in protecting the body against oxidative damage and decreasing reactive oxygen species (ROS).[18]

Limitations of this study include the unavailability of factors such as the subject's detailed dietary intake that may affect the zinc levels in blood. The relatively small sample size and short duration of the study is also a drawback for this study. Future trials with longer duration to include larger sample size and to monitor food intake may be done to limit these confounders on whole blood zinc levels.

Conclusion

In summary, whole blood zinc level was associated with the severity of acne vulgaris in the Filipino population. Whole blood zinc levels showed inverse correlation with acne vulgaris severity, with lower zinc levels correlated with higher severity of acne vulgaris. Further studies are needed to determine the role of zinc in the pathogenesis of acne vulgaris. Randomized placebo-controlled clinical trials are necessary to determine the effects of oral zinc supplementation on acne vulgaris patients.

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