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ORIGINAL ARTICLE

A Correlation between Serum Level of Alkaline Phosphatase and Acne Severity in Children and Adolescents: A Retrospective Cross-Sectional Study

Mihn-Sook Jue, Eunjung Park, Ho Song Kang[1], Joung Soo Kim[2]

Department of Dermatology, Veterans Health Service Medical Center, [1]Department of Medicine, Hanyang University Graduate School, Seoul, [2]Department of Dermatology, Hanyang University Guri Hospital, Guri, Korea

Background: Acne is a chronic inflammatory disease of the pilosebaceous unit and usually affects adolescents when the peak concentrations of growth hormone, insulin-like growth factor 1, and androgen are demonstrated. The activity of alkaline phosphatase (ALP), which increases physiologically in growing children and adolescents, in the pilosebaceous unit has been reported. However, the correlation between the serum level of ALP and the number of acne lesions has not been studied. **Objective:** The present cross-sectional study was designed to evaluate the correlation between serum level of ALP and the numbers of non-inflammatory and inflammatory acne lesions in children and adolescents. **Methods:** For this study, 202 pediatric and adolescent patients clinically diagnosed with acne vulgaris were included. Age, sex, serum level of ALP, number of non-inflammatory acne lesions, number of inflammatory acne lesions, and number of total acne lesions were evaluated. Additionally, the serum level of dehydroepiandrosterone sulfate was evaluated in 117 patients. Multiple regression analysis was performed. Multicollinearity was quantified using the variance inflation factor. **Results:** In the 202 patients, serum level of ALP was the only independent factor that significantly affected both the number of non-inflammatory acne lesions and of total acne lesions (regression coefficient = 0.089 and 0.086, respectively, $p < 0.001$). **Conclusion:** There was a significant correlation between serum level of ALP and the extent of acne (non-inflammatory acne lesions and total acne lesions). **(Ann Dermatol 32(3) 206～212, 2020)**

-Keywords-
Acne vulgaris, Adolescent, Alkaline phosphatase, Child, Dehydroepiandrosterone sulfate

INTRODUCTION

Acne vulgaris is a common disorder of the pilosebaceous unit seen mainly in adolescents. The four important pathogeneses of the disorder are (1) abnormal follicular keratinization, (2) excess sebum production, (3) inflammation, and (4) the presence and activity of *Propionibacterium acnes*[1]. Although the exact pathophysiologic mechanism of acne development is not clear, the inciting event is believed to result from stimulation of the pilosebaceous units by circulating androgens. The production of sebum leads to retention in hyperkeratotic infundibulum, which blocks and dilates the follicular infundibulum, resulting in the formation of a comedone[2,3]. Dehydroepiandrosterone sulfate (DHEA-sulfate), which originates in the adrenal gland, is the major adrenal androgen precursor and gradually increases during puberty[4]. Previous studies have revealed greater values of hyperandrogenism in pathogenesis of acne, and several studies about the relationship between serum level of DHEA-sulfate and severity of acne have been reported[5-9]. Alkaline phosphatase (ALP) is a mixture of isozymes and known to be associated with bone, liver, and

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Corresponding author: Joung Soo Kim, Department of Dermatology, Hanyang University Guri Hospital, 153 Gyeongchun-ro, Guri 11923, Korea. Tel: 82-31-560-2284, Fax: 82-31-557-4872, E-mail: tuentuen@hanyang.ac.kr
ORCID: https://orcid.org/0000-0002-3014-9645

intestine. Because of this association, the serum level of ALP is used to distinguish between normal and pathologic states of these organs[10]. This enzyme is increased physiologically in growing children and adolescents and the serum level of ALP reflects pubertal growth and correlate with sexual maturity in adolescents[11,12]. Maximum sebum production begins during puberty, which coincides with an increased level of ALP[13,14]. In addition, ALP is also distributed in human sebaceous glands[15]. There have been reports investigating the correlation between acne and serum levels of insulin-like growth factor 1, growth hormone, and androgens including DHEA-sulfate all of which increase physiologically in growing children and adolescents[9]. However, the serum level of ALP was only evaluated as a hepatic panel for laboratory monitoring during isotretinoin treatment and has not been studied for its association with number of acne lesions[16]. The present study was designed to evaluate the correlation between serum level of ALP and the numbers of non-inflammatory and inflammatory acne lesions in children and adolescents. We also evaluated the relationship between DHEA-sulfate, which has been shown to have an association with acne severity in previous studies and ALP[5-9].

MATERIALS AND METHODS

From 2011 to 2015, children and adolescents aged 8 to 18 years with clinically diagnosed acne vulgaris at the Department of Dermatology, Hanyang University Guri Hospital were included in this retrospective study. This study was approved and monitored by Institutional Review Board (IRB) of Hanyang University Guri Hospital (IRB No. 2018-08-029-001). All data were fully anonymized before we assess them, and the IRB waived the requirement for informed consent. Patients who had a history of systemic antibiotics or retinoid treatment, which can influence ALP level, had endocrine diseases including congenital adrenal hyperplasia and polycystic ovary syndrome, or had possible conditions of elevated ALP such as hepatobiliary disease or primary bone disease were excluded from the study. Demographics and clinical data, such as age, sex, numbers of non-inflammatory acne lesions and inflammatory acne lesions, number of total acne lesions, and serum level of ALP were measured in 202 patients. Additionally, the serum level of DHEA-sulfate was measured in 117 patients. In this retrospective study, the numbers of non-inflammatory and inflammatory acne lesions of the whole face were counted by two different investigators based on clinical photos, and the total number of acne lesions was then determined. Non-inflammatory lesions consist of white and black comedones, and inflammatory lesions include erythematous papules, pustules, and nodules. The serum level of ALP was determined by the Beckman Coulter analyzer (Beckman Coulter Inc., Brea, CA, USA). This method was based on the recommendations of the German Society for Clinical Chemistry (GSCC)[17]. ALP activity was determined by measuring the rate of conversion of 4-nitrophenyl phosphate (4-NPP) to 4-nitrophenol (4-NP) in the presence of magnesium ions and diethanolamine as phosphate acceptors at pH 9.8[14]. The rate of increase in absorbance due to the formation of 4-NP was measured at 410/480 nm and was directly proportional to the ALP activity in a sample. The serum level of DHEA-sulfate was determined by the r-Counter (CoBRA 5010 series Quantum®; Packard Inc., Palo Alto, CA, USA). This method is based on radioimmunoassay and a DHEA-sulfate RIA CT kit® (IBL International, Hamburg, Germany) that is used for the radioimmunoassay. Data were analyzed using IBM SPSS ver. 22.0 for Windows (IBM Corp., Armonk, NY, USA). Multiple linear regression analysis was used to identify the factors significantly affecting the number of acne lesions. Multicollinearity of independent variables was assessed via the variance inflation factor (VIF) statistic. If VIF value exceeding 5.0, there is a problem with multicollinearity. The examined factors included age, sex, serum levels of ALP and DHEA-sulfate, number of non-inflammatory acne lesions, number of inflammatory acne lesions, and total number of acne lesions. Simple linear regression analysis was used to evaluate the relationship between serum level of ALP and DHEA-sulfate. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Demographic analysis

Demographic and descriptive variables are shown in Table 1.

Table 1. Demographics and descriptive variables of the study patients

Variable	Value
Age (yr)	13.09±3.18
Sex	
Male	113 (55.94)
Female	89 (44.06)
Alkaline phosphatase (U/L)	164.52±90.44
DHEA-sulfate (μg/dl, n=117)	256.97±100.71
Non-inflammatory acne lesion	21.61±10.47
Inflammatory acne lesion	17.02±8.80
Total acne lesions	38.63±14.84

Values are presented as mean±standard deviation or number (%). DHEA: dehydroepiandrosterone.

A total of 202 patients diagnosed with acne vulgaris were included in this study. Of the 202 patients, 113 (55.94%) were male and 89 (44.06%) were female. The age range of the patients was between 8 and 18 years with a mean age of 13.09±3.18 years. The level of ALP ranged from 39~439 U/L with a mean level of 164.52±90.44 U/L. The level of DHEA-sulfate ranged from 69~547 μg/dl with a mean level of 256.97±100.71 μg/dl. The number of non-inflammatory acne lesions ranged from 5~51 with a mean of 21.61±10.47, and the number of inflammatory acne lesions ranged from 2~42 with a mean of 17.02±8.80. The number of total lesions ranged from 11~82 with a mean of 38.63±14.84.

Analysis of factors contributing to the number of acne lesions in 202 patients

Serum level of ALP was an independent factor significantly affecting the number of non-inflammatory acne lesions ($p<0.001$). The regression coefficient of this factor was 0.089. Similarly, serum level of ALP was a significant factor affecting the number of total acne lesions ($p<0.001$). The regression coefficient of this factor was 0.086. There was no independent factor significantly affecting the number of inflammatory acne lesions. Other variables including age and sex did not show any significant results in the analyses (Table 2, a model 1 in Fig. 1~3).

Analysis of factors contributing to the number of acne lesions including DHEA-sulfate in 117 patients

Serum level of ALP was a significant independent factor affecting the number of non-inflammatory and total acne lesions ($p<0.001$ and $p=0.001$, respectively). The regression coefficients of these factors were 0.078 and 0.067, respectively. The serum level of DHEA-sulfate was a significant independent factor affecting all dependent variables including numbers of non-inflammatory, inflammatory, and total acne lesions ($p<0.001$, $p=0.004$, and $p<0.001$, respectively). The regression coefficients of these factors were 0.033, 0.028, and 0.061, respectively. Other variables including age and sex did not show significant results in any analyses (Table 3, a model 2 in Fig. 1~3).

Analysis of correlation between serum levels of ALP and DHEA-sulfate

There was a significant correlation between serum levels of ALP and DHEA-sulfate (regression coefficient=0.580, $p<0.001$; Table 4).

DISCUSSION

Acne is a common skin condition that usually begins in adolescence and often resolves in early adulthood[1]. It is a chronic inflammatory disease of the sebaceous glands, which become blocked and inflamed to varying degrees[1,2]. The pathophysiology is still not totally understood, but it is assumed to be related in part to excess sebum production, abnormal follicular keratinization, microbial colonization by *P. acnes*, and inflammation[18]. ALP is a group of cell membrane metalloenzymes that catalyzes the alkaline hydrolysis of phosphate esters, generating an organic radical and inorganic phosphate and regulates the transportation of fats, calcium, proteins, carbohydrates, and sodium and potassium ions[19,20]. ALP activity is widely expressed in actively proliferating tissues with a high metabolic rate such as bone, liver, mucosa of the small intestine and proximal convoluted tubules of the kidney, and the placenta[21]. Some

Table 2. Factors contributing to the number of acne lesions in acne patients (n=202)

Variable	Regression coefficient (SE)†	Standardized regression coefficient	*p*-value	VIF
Non-inflammatory acne lesion				
Age	0.273 (0.246)	0.083	0.269	2.227081
Sex	0.549 (1.089)	0.026	0.615	1.061908
Alkaline phosphatase	0.089 (0.009)	0.768	<0.001*	2.315278
Inflammatory acne lesion				
Age	0.017 (0.292)	0.006	0.953	2.227081
Sex	−1.465 (1.290)	−0.083	0.257	1.061908
Alkaline phosphatase	−0.004 (0.010)	−0.038	0.727	2.315278
Total acne lesions				
Age	0.290 (0.432)	0.062	0.502	2.227081
Sex	−0.916 (1.908)	−0.031	0.632	1.061908
Alkaline phosphatase	0.086 (0.016)	0.522	<0.001*	2.315278

SE: standard errors, VIF: variance inflation factor. *Significant at $p<0.05$. †The regression coefficient are estimated for each 10 unit increase of alkaline phosphatase (U/L) and dehydroepiandrosterone sulfate (μg/dl).

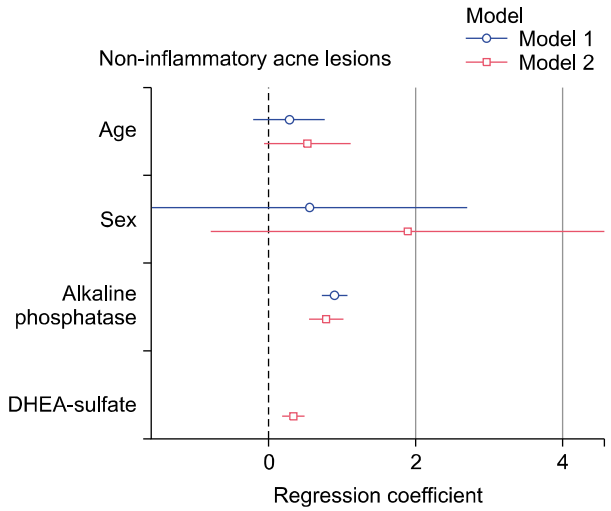

Fig. 1. Regression coefficient for non-inflammmatory acne lesions. Model 1 is the result of 202 patients who measured only serum level of alkaline phosphatase. Model 2 is the result of 117 patients who measured both serum level of alkaline phosphatase and dehydroepiandrosterone (DHEA)-sulfate.

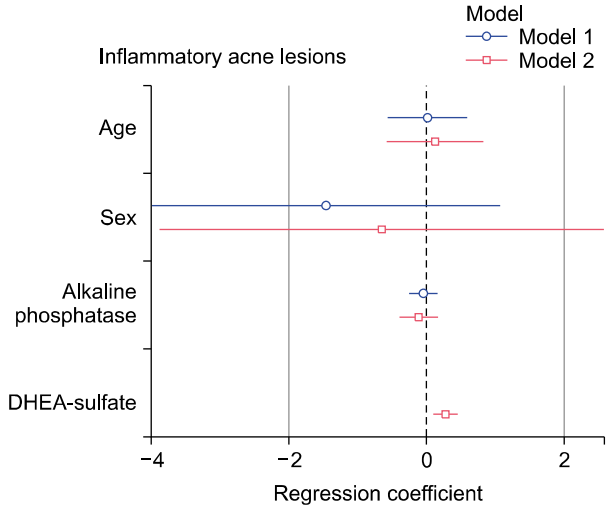

Fig. 2. Regression coefficient for inflammmatory acne lesions. Model 1 is the result of 202 patients who measured only serum level of alkaline phosphatase. Model 2 is the result of 117 patients who measured both serum level of alkaline phosphatase and dehydroepiandrosterone (DHEA)-sulfate.

ALP released from these tissues constitutes the total amount measured in the blood[21]. Since ALP is a marker of osteoblastic activity, growing children have higher levels than fully grown individuals[11]. The highest levels of ALP are detected during the rapid growth phases of childhood such as infancy and puberty[8]. Elevated level of ALP correlates with sex maturity rating, whereas pubertal maturation is correlated with prevalence and severity of acne[9,22]. It has been reported that the pilosebaceous unit displays

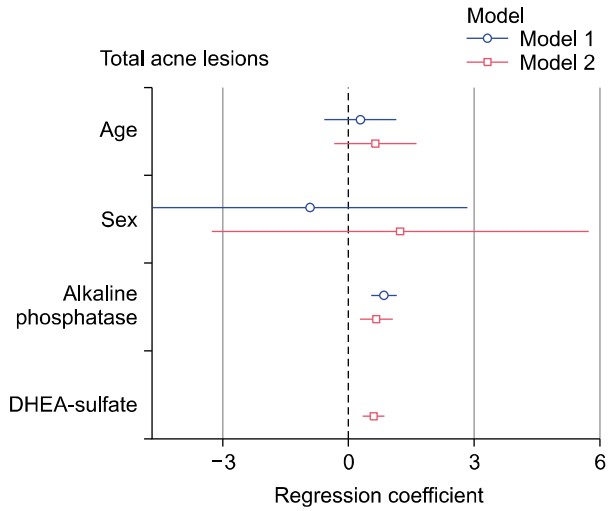

Fig. 3. Regression coefficient for total acne lesions. Model 1 is the result of 202 patients who measured only serum level of alkaline phosphatase. Model 2 is the result of 117 patients who measured both serum level of alkaline phosphatase and dehydroepiandrosterone (DHEA)-sulfate.

prominent ALP activity and ALP is identified as a critical marker for hair growth promotion[20,23]. The sebaceous gland normally has a high level of endogenous ALP activity, and ALP activity in the sebaceous gland was substantially diminished with reduced lipid content after cooling damage to the sebaceous gland in a murine model[24]. These findings may not clarify the role of ALP activity in the physiology of the sebaceous gland but do suggest that ALP activity reflects the activity of the sebaceous gland. From such evidence, the author hypothesized that serum level of ALP could reflects the state of the sebaceous gland, and that elevated level of ALP may play a role in the prediction of acne severity.

The results showed that serum level of ALP significantly correlated with the number of non-inflammatory and total acne lesions, but no correlation between ALP level and number of inflammatory acne lesions was exhibited. Elevated ALP may be associated with non-inflammatory acne lesions as a consequence of its association with sebum, which is mainly synthesized by the sebaceous glands. The sebaceous gland is believed to be affected in a relatively early stage of acne pathophysiology and excessive sebum production is considered as one of the most important promoters of comedogenesis[2,3,25]. Some authors showed a significant correlation between closed comedones and sebum[26]. Therefore, ALP might play a role in hyperseborrhea, which increases the number of acne lesions, and the results that showed the correlation between ALP and DHEA-sulfate further support this theory. However, hyperseborrhea itself does not explain the significant relation-

Table 3. Factors contributing to the number of acne lesions including dehydroepiandrosterone sulfate (DHEA-sulfate) in acne patients (n=117)

Variable	Regression coefficient (SE)†	Standardized regression coefficient	*p*-value	VIF
Non-inflammatory acne lesion				
Age	0.523 (0.296)	0.163	0.080	2.339652
Sex	1.887 (1.350)	0.088	0.165	1.099286
Alkaline phosphatase	0.078 (0.012)	0.681	<0.001*	2.916866
DHEA-sulfate	0.033 (0.008)	0.314	<0.001*	1.499761
Inflammatory acne lesion				
Age	0.129 (0.357)	0.050	0.718	2.339652
Sex	−0.648 (1.629)	−0.038	0.691	1.099286
Alkaline phosphatase	−0.011 (0.014)	−0.119	0.442	2.916866
DHEA-sulfate	0.028 (0.009)	0.328	0.004*	1.499761
Total acne lesions				
Age	0.652 (0.499)	0.145	0.194	2.339652
Sex	1.239 (2.275)	0.041	0.587	1.099286
Alkaline phosphatase	0.067 (0.020)	0.419	0.001*	2.916866
DHEA-sulfate	0.061 (0.013)	0.414	<0.001*	1.499761

SE: standard errors, VIF: variance inflation factor. *Significant at $p<0.05$. †The regression coefficient are estimated for each 10 unit increase of alkaline phosphatase (U/L) and DHEA-sulfate (μg/dl).

Table 4. Correlation between alkaline phosphatase and dehydroepiandrosterone sulfate in acne patients (n=117)

Variable	Regression coefficient (SE)	Standardized regression coefficient	*p*-value
Alkaline phosphatase	0.580 (0.085)	0.537	<0.001*

SE: standard errors. *Significant at $p<0.05$.

ship with only the non-inflammatory lesions and not the inflammatory lesions. This can be explained by a number of recently reported studies on abnormality of sebum lipid in acne patients. These studies indicate that alteration of certain sebum components provokes reactive follicular hyperkeratosis and comedone formation or induces the follicular inflammation reaction[27,28]. Increased activation of ALP may play a role in a change of sebaceous lipid that mainly leads to comedogenesis. Inflammation and oxidative stress are the one of the earliest events in acne process and can build the foundations for acne to occur, causing all the pathogenic stages to initiate. Recently, López-Posadas et al.[29] demonstrated that oxidative stress causes a distinct increase in ALP activity with cell toxicity in enterocyte which suggests that ALP activity may reflects the burden of oxidative stress. Thus, elevated level of ALP may reflect the increased burden of cutaneous or systemic oxidative stress which is known to the representative as a starter gun in However, whether level of serum ALP may have intercorrelation with the pilosebaceous ALP activity or burden of cutaneous or systemic oxidative stress should be validated though further studies.

Based on the pathophysiologies of acne, correlations between androgens including DHEA-sulfate, 17-hydroxyprogesterone, testosterone, and free testosterone and the severity of acne have been reported[5-9]. Androgens play an essential role in increasing the size of the sebaceous glands, stimulating sebum production and stimulating keratinocyte proliferation in the ductus seboglandularis and acroinfundibulum[8]. This correlation is supported by the finding that conditions of androgen excess or the presence of hyperandrogenism in the forms of congenital adrenal hyperplasia, adrenal tumors, polycystic ovary disease, and ovarian tumors are associated with severe acne[1]. Similarly, a statistically significant correlation between serum level of DHEA-sulfate and acne lesion count was found in this study. This finding supports the previously described relationship between severity of acne and DHEA-sulfate.

In this study, gender did not show a significant correlation with number of acne lesions. This finding differs from previous studies, which have suggested that male subjects tend to have a greater acne severity grade than females because of the difference in the levels of androgens and skin pH[30-33]. It appears that the difference in the study findings resulted from the small sample size in the present study and the gap of the acne severity index. Also, there is no

correlation between age and acne lesion count in this study. This factor suggests that acne severity may be associated with pubertal maturation rather than chronological age.

This is the first report identifying the correlation between serum ALP and acne lesions, but there are some limitations. First, this study was conducted with a retrospective design and a study population from a particular geographic area that may not generalize to all populations. Second, although the levels of serum ALP and DHEA-sulfate depend largely on age and sex, we did not compare subjects with acne to age- and sex-matched controls without acne. To compensate for this problem, we used multiple linear regression models to adjust for potential confounding factors, including age and sex. Future large, randomized, controlled, and multicenter trials are required to elucidate more precise correlations. Lastly, there is a possibility of underestimation of acne lesions, especially non-inflammatory ones, due to the limitation of numbering based on photos. This implies that the number of lesions counted by inspection of clinical photos includes only visible lesions, not microcomedones which can't be detected by naked eyes.

In conclusion, this study showed that serum level of ALP, which is one of the commonly investigated enzymes in routine clinical chemistry laboratories, correlates with number of non-inflammatory acne lesions in children and adolescents. These results suggest that there should be profound attempt to evaluate the comedones such as skin stretching and it can be effective to consider a particularly effective treatment for non-inflammatory acne lesion, both treatment and prevention purpose, in acne patients with elevated ALP level.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ORCID

Mihn-Sook Jue, https://orcid.org/0000-0002-8253-6188
Eunjung Park, https://orcid.org/0000-0002-4580-0154
Ho Song Kang, https://orcid.org/0000-0003-4257-2560
Joung Soo Kim, https://orcid.org/0000-0002-3014-9645

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