Original Article

Comparison of Serum Dehydroepiandrosterone Sulfate, Testosterone, and Dihydrotestosterone Levels in Males with Various Degrees of Acne Vulgaris Severity

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Abstract

Objective: This study compared the levels of dehydroepiandrosterone (DHEA) sulfate, testosterone, and dihydrotestosterone (DHT) in the serum of men with various degrees of severity grading of acne vulgaris. **Methods:** We conducted a cross-sectional analytic observational study and used the Combined Acne Severity Classification. Serum DHEA sulfate (DHEAS), testosterone, and DHT levels were measured by enzyme-linked immunosorbent assay. We recruited 63 males with acne vulgaris. **Results:** For mild, moderate, or severe acne, the mean serum level of DHEAS was 90.92, 153.54, and 166.67 ng/ml ($P = 0.000$); testosterone was 6.66, 8.11, and 8.97 ng/ml ($P = 0.445$); and DHT was 87.33, 111.72, and 124.71 ($P = 0.01$), respectively. *Post hoc* analysis showed significant differences for DHEAS and DHT serum levels. There were significant differences for DHEAS and DHT serum levels. **Conclusion:** There was no significant difference in serum testosterone levels between groups, although there was an increase in concentration by acne vulgaris severity.

Keywords: Acne vulgaris, degree of severity, dehydroepiandrosterone sulfate, dihydrotestosterone, testosterone

Introduction

Acne vulgaris is a chronic inflammatory skin condition that primarily occurs in the pilosebaceous unit, characterized by the appearance of comedones, papules, pustules, nodules, and cysts.[1,2] It is the most common skin problem of young people aged 12–24 years.[1,3,4] While the onset of acne vulgaris in women is faster than in men, the severity is higher in men than in women. The main reason for this phenomenon is probably due to higher levels of sebum and androgen hormones in males.[5-8] The prevalence of acne vulgaris, based on the previous study held in Palembang, Indonesia, was reported to be about 68.2%.[5] A hospital study in India obtained 309 acne vulgaris patients from 28,197 new patients who attended a dermatology outpatient unit between August 2006 and June 2008.[6] Further, the prevalence of acne vulgaris in a cross-sectional study in Yazd, Iran, was 85.9%.[8]

The pathogenesis of acne vulgaris is comprised of increased production of sebum, follicular hyperkeratinization, *Propionibacterium acnes* proliferation, and inflammation.[8,9] Two of these four factors, increased production of sebum and follicular hyperkeratinization, are highly correlated with androgen hormone stimulation.[7,10] Androgen hormones consist of the inactive precursor, such as dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androsterone. Testosterone and dihydrotestosterone (DHT) are the two most potent androgen hormones.[1,7,10] Evidence has shown a correlation between DHEAS and DHT levels with the number of acne vulgaris lesions in adult women.[11]

The determination of the severity level of acne vulgaris is varied and is based on the number and type of lesions; however, no single assessment criteria have ever been deemed the gold

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standard. The Combined Acne Severity Classification (CASC), one of the criteria used to determine the severity level of acne vulgaris, divides acne vulgaris into three levels: mild, moderate, and severe.[12,13]

Androgen hormones affect skin appendages, such as a sebaceous gland, that are involved in acne vulgaris pathogenesis and which appear to be dependent on biologically active androgens. DHEAS is considered the most important regulator of sebum secretion. Sebocytes will convert DHEAS into a more potent androgen, such as testosterone and DHT. The purpose of this study was to investigate which androgen hormones effect on acne vulgaris pathogenesis. The result of this study will provide an important contribution in which androgen hormones will be modified to affect acne vulgaris progression. The study aimed to compare the levels of DHEAS, testosterone, and DHT in serum from males with various degrees of severity grading of acne vulgaris.

Methods

Study design and subjects

This cross-sectional observational study involved males, aged 13–30 years, with various degrees of acne vulgaris severity, who were divided into mild, moderate, and severe groups. Each participant signed informed consent for medical treatment and any study approach. This study was approved by the Ethical Committee of Health Study of Regional General Hospital and Dr. Saiful Anwar Malang as written in the letter of ethical approval no. 400/97/K.3/302/2015, no. 400/66/K.3/302/2015, and no. 400/94/K.3/302/2015. Sample size calculation used the Lemeshow formula (n = [Zα2 p (1-p)]/d2) to determine a minimum sample size of 19 males for each severity group.

The exclusion criteria consisted of receiving topical therapy, such as antibiotics, benzoyl peroxide, tretinoin, adapalene, and other keratolytics (salicylic acid and sulfur). The topical treatment was given within 2 weeks. Subject with treatments that affect the activity of androgen hormone and pathogenesis of acne vulgaris, such as an oral retinoid, systemic antibiotic, spironolactone, corticosteroid and finasteride, and acneiform eruption-related drugs such as lithium, halogen, isoniazid, phenytoin, Vitamin B within 1 month before study must be excluded. Individuals were also excluded if their body mass index was >25.

Classification of acne vulgaris severity level

The severity level assessment was based on the CASC method and conducted by three examiners, in a subsequent order, on the same day. CASC divides acne vulgaris into three levels: mild, moderate, and severe. Criteria for mild acne were a Comedones count of <20, inflammatory lesion count of <15, or a total lesion count of <30. Criteria for moderate acne were a comedone count of 20–100, an inflammatory lesion count of 15–50, or a total lesion count between 30 and 125. Criteria for severe acne were a cyst count of >5, a comedone count of >100, an inflammatory lesion count of >50, or a total lesion count of >125.[12,13]

Hormone examination

Hormone concentration was measured from blood samples. The evaluations of serum DHEAS, testosterone, and DHT levels were conducted using an enzyme-linked immunosorbent assay (ELISA). Five milliliters of blood was taken from the middle cubital vein using Venoject and then put into a nonadditive Vacutainer and allowed to thicken. The blood was centrifuged, and the serum was collected and stored at −10°C. An ELISA was done following the accomplishment of all study participants. An Elabscience ELISA kit was used to measure serum DHEAS and DHT levels, and a Cusabio ELISA kit was used to measure serum testosterone levels. Hormone levels were obtained from the measurement of optical density at a 450-nm wavelength using a microplate reader.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 22, (IBM, 1 New Orchard Road Armonk, New York 10504-1722 United States). The Kolmogorov–Smirnov test was used to evaluate the normality of data distribution. Homogeneity data evaluation was performed using Levene's test. One-way ANOVA was performed to detect the differences of the mean DHEAS, testosterone, and DHT levels between each acne severity level in normally distributed data. *Post hoc* analysis was also done if there was a significant difference in the mean difference test.

Results

This study involved 63 men with acne vulgaris. This study evidenced a significant difference of average age in various severity levels of acne vulgaris [Table 1].

The average age of patients with mild acne vulgaris was 22.71 years, moderate acne vulgaris was 23.29 years, and severe acne vulgaris was 19.24 years. The Kolmogorov–Smirnov test showed a standard distribution of serum DHEAS testosterone and DHT levels ($P > 0.05$). Levene's test showed homogeneity variation in data for serum DHEAS, testosterone, and DHT levels ($P > 0.05$) [Table 1]. This study fulfilled all the criteria for one-way ANOVA.

Table 1: Age characteristics, serum hormone mean distribution, and variation

Characteristics	Categories	Value	*P*
Average age (years)	Mild acne vulgaris	22.71	0.000
	Moderate acne vulgaris	23.29	
	Severe acne vulgaris	19.24	
Kolmogorov-Smirnov test	DHEAS	1.140	0.149
	Testosterone	1.145	0.100
	DHT	1.034	0.235
Levene's test	DHEAS	2.827	0.067
	Testosterone	0.002	0.998
	DHT	2.839	0.091

DHEAS: Dehydroepiandrosterone sulfate, DHT: Dihydrotestosterone

Hormone level comparison for various severity levels of acne vulgaris

The average level of serum DHEAS, testosterone, and DHT was elevated in concordance with an increased severity level of acne vulgaris. The one-way ANOVA test showed a significant difference between serum DHEAS and DHT in various severity levels of acne vulgaris ($P < 0.05$). There was no significant difference in testosterone levels between each severity level of acne vulgaris [Table 2].

Post hoc analysis

Post hoc analysis displayed significant differences in serum DHEAS and DHT mean levels between mild and moderate acne vulgaris and between mild and severe acne vulgaris ($P < 0.05$). *Post hoc* testing did not demonstrate significant differences in the mean level of serum DHEAS and DHT between moderate acne vulgaris and severe acne vulgaris [Table 3].

Discussion

Acne vulgaris is a common skin disorder that affects teenagers and young adults. Epidemiological data show that 80% of acne vulgaris patients fall within the range of 11–30 years of age.[14] A descriptive study from the United States of America showed that the average age of acne vulgaris was 25 years.[15] On the other hand, a study in Hong Kong evidenced the age range for acne vulgaris as 15–25 years.[16] The average age of participants in this study [Table 1] was at the second decades and similar to previous studies.

Table 2: Comparison of serum dehydroepiandrosterone sulfate, testosterone, and dihydrotestosterone levels (mean±standard deviation)

Variables	Severity level of AV			*P*
	Mild	Moderate	Severe	
DHEAS	90.927±36.128	153.546±66.775	166.376±52.826	0.000
Testosterone	6.66±5.28	8.11±6.19	8.97±6.19	0.445
DHT	87.33±19.5	111.72±35.98	124.71±37.19	0.001

DHEAS: Dehydroepiandrosterone sulfate, DHT: Dihydrotestosterone, AV: Acne vulgaris

Table 3: *Post hoc* analysis of serum dehydroepiandrosterone sulfate and dihydrotestosterone mean comparison

Variables	Severity level	Mean	*P*
DHEAS	Mild	90.927±36.128	0.001
	Moderate	153.546±66.775	
	Mild	90.927±36.128	0.000
	Severe	166.376±52.826	
	Moderate	153.546±66.775	0.718
	Severe	166.376±52.826	
DHT	Mild	87.33±19.5	0.042
	Moderate	111.72±35.98	
	Mild	87.33±19.5	0.001
	Severe	124.71±37.19	
	Moderate	111.72±35.98	0.391
	Severe	124.71±37.19	

DHEAS: Dehydroepiandrosterone sulfate, DHT: Dihydrotestosterone

Severe acne vulgaris tends to occur in younger individuals. Acne vulgaris lesions are commonly said to act as predictors of the onset of puberty and are inclined to become more severe at a younger age than older.[6,7,15] Some studies showed that acne vulgaris would eventually regress in the patients' mid-20s or 30s and few will get acne vulgaris in their 40s.[6,15] Teenagers endure hormonal changes related to puberty and gonads; thus, they have increased production and secretion of androgen hormones.[17,18] Androgen hormones, such as DHEAS, testosterone, and DHT, are all known to be involved in gene arrangement, especially in genes responsible for the development of sebaceous glands and sebum production.[19,20] A prevalence study of acne vulgaris in Iran revealed that moderate and severe acne were more frequent in males than in females, although total prevalence was more frequent in females.[8] Estrogen has a protective effect against acne vulgaris in females. The effect of estrogen in acne vulgaris occurs through several mechanisms, such as a direct opposition effect on androgens, inhibition of androgen secretion, or modulating genes involved in sebaceous gland growth and function.[19,20]

The mechanism for increasing androgen hormone levels that result in the enlargement and overstimulation of sebaceous glands is still unknown.[17,19] As a precursor, DHEAS hormone will be altered into testosterone and then DHT, which subsequently binds the androgen receptor in sebocytes, follicular and epidermal keratinocytes, sweat glands, and probably, dermal papillary cells.[19,21] The androgen receptor is a nuclear receptor with a transcriptional propensity to reach its biologic effect.[21] DHT-androgen receptor binding interacts with deoxyribonucleic acid and arranges the genes involved in sebaceous cell proliferation and lipogenesis.[19] Androgen hormones play a critical role in follicular hyperkeratinization and affect sebum production of sebaceous glands.[17,20] The process above will result in an oversecretion of sebum, accompanied by cell accumulation on the skin's surface, thus blocking sebaceous gland estuaries. Clogged sebaceous gland estuaries will lead to dilation of the upper part of hair follicles and finally the formation of microcomedones.[7,17] These microcomedones will get bigger and, in addition to the increased proliferation of *Propionibacterium acnes*, causes the rupture of the follicular wall. It releases sebum, keratin, and bacteria into the dermis and stimulates an inflammatory response.[7,17]

The DHEAS hormone is a weak androgen precursor. Sebocytes and a small population of dermal papillary cells have the enzymatic capacity to transform DHEAS into another androgen with higher potency.[21] DHEAS hormone is majorly synthesized in the adrenal glands and reaches the skin through the blood vessels. This hormone is the most detected androgen in circulation, with relatively constant levels detected in both genders.[10,17,21,22] A study in Iraq successfully measured serum

DHEAS levels using the ELISA method in males with different levels of acne vulgaris severity. This study showed that the average level of serum DHEAS was significantly higher in the severe acne vulgaris group (4.05 ± 0.96 μg/ml) compared to the control (2.90 ± 0.27 μg/ml), mild (2.38 ± 0.46 μg/ml), and moderate (2.73 ± 0.63 μg/ml) groups.[23] Our study indicated that mean DHEAS levels increased by increasing acne vulgaris severity grade [Table 2]. There was a significant difference in mean serum DHEAS levels when comparing mild versus moderate acne vulgaris, as well as between mild and severe acne vulgaris [Table 3].

DHT is the most potent androgen-inducing keratinocyte hyperproliferation. The level of DHT hormone is lower than testosterone in both tissues and circulation. DHT binds androgen receptors with a higher affinity than testosterone. The bond between DHT and androgen receptors is more stable and thus more effective at increasing sebum production.[24] The elevation of DHT levels in infundibular keratinocytes leads to follicular hyperkeratinization.[7,25] The previous study showed a correlation coefficient of 0.75 with a significance level of 0.001 DHT level on female acne vulgaris group with either inflammatory or noninflammatory acne vulgaris lesion count.[11] Our study showed an increase in serum DHT levels that correlated with increasing acne vulgaris severity grade [Table 2]. There was a significant difference in mean serum DHT levels between mild and moderate acne vulgaris and between mild and severe acne vulgaris [Table 3].

The testosterone hormone induces the enlargement and secretion of sebaceous glands through binding with androgen receptors.[7,26] Testosterone also increases the proliferation of follicular keratinocytes.[3,7] Follicular hyperkeratinization causes pilosebaceous canal clogging and eventually development of microcomedones as an early lesion of acne vulgaris.[3,7,27] Our study showed no significant differences in mean serum testosterone levels between the three acne vulgaris severity groups, although increasing testosterone levels did trend with increasing the acne vulgaris severity grade [Table 2]. Blood testosterone concentrations are affected by various factors, which were not excluded from this study. Testosterone is often measured from human blood (serum), though some circulating testosterone fractions will be bound to albumin.[28,29] Blood testosterone concentrations are influenced by sleep duration and nicotine use.[29] Testosterone has low diurnal variation in Asian individuals.[30] In 2011, Ewadh demonstrated a significant difference in testosterone levels when comparing males with or without acne vulgaris.[17] A previous study by Miranti also showed that serum testosterone levels in females with severe acne vulgaris were higher than in those with mild acne vulgaris, though some of the results were not statistically significant.[31]

Conclusion

This study displayed significant differences of serum DHEAS and DHT levels between mild and moderate acne vulgaris, as well as between mild and severe acne vulgaris. Serum testosterone levels, though not significantly different, became elevated as the severity level of acne vulgaris increased. Therefore, our suggestion for future studies would be to investigate the correlation between each serum androgen concentration and counts of comedones, erythematous papules, pustules, or cyst nodule lesions.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ebede TL, Arch EL, Berson D. Hormonal treatment of acne in women. J Clin Aesthet Dermatol 2009;2:16-22.
2. Lai KW, Mercurio MG. Update of the treatment of acne vulgaris. J Clin Outcomes Manage 2009;16:115-26.
3. Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. J Am Acad Dermatol 2003;49:S200-10.
4. Ali SM, Khan M, Samdani AJ, Siddiqui A. Study to assess the effect of topical clindamycin gel in acne vulgaris. Pak J Pharm Sci 2010;27:15-9.
5. Tjekyan RM. Acne vulgaris and its risk factors. Media Medika Indones 2008;43:37-43.
6. Adityan B, Thappa DM. Profile of acne vulgaris – A hospital-based study from South India. Indian J Dermatol Venereol Leprol 2009;75:272-8.
7. Zanglein AL, Graber EM, Thiboutot DM. Acne vulgaris and acneiform eruptions. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: McGraw-Hill; 2012. p. 897-917.
8. Noorbala MT, Mozaffany B, Noorbala H. Prevalence of acne and its impact on the quality of life in high school-aged adolescent in Yazd, Iran. J Pak Assoc Derma 2013;23:168-72.
9. Well D. Acne vulgaris: A review of causes and treatment options. Nurse Pract 2013;38:22-31.
10. Harper JC. Hormonal therapy for acne using oral contraceptive pills. Semin Cutan Med Surg 2005;24:103-6.
11. Cappel M, Mauger D, Thiboutot D. Correlation between serum levels of insulin-like growth factor 1, dehydroepiandrosterone sulfate, and dihydrotestosterone and acne lesion counts in adult women. Arch Dermatol 2005;141:333-8.
12. Lehmann HP, Robinson KA, Andrews JS, Holloway V, Goodman SN. Acne therapy: A methodologic review. J Am Acad Dermatol 2002;47:231-40.
13. Liao DC. Management of acne. J Fam Pract 2003;52:43-51.
14. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, *et al.* Management of acne: A report from a global alliance to improve outcomes in acne. J Am Acad Dermatol 2003;49:S1-37.
15. Yentzer BA, Hick J, Reese EL, Uhas A, Feldman SR, Balkrishnan R, *et al.* Acne vulgaris in the United States: A descriptive epidemiology. Cutis 2010;86:94-9.
16. Yeung CK, Teo LH, Xiang LH, Chan HH. A community-based epidemiological study of acne vulgaris in Hong Kong adolescents. Acta Derm Venereol 2002;82:104-7.
17. Ewadh MJ, Shemran KA, Al-Hamdany KJ. The correlation of some hormones with acne vulgaris. Int J Sci Nat 2011;2:713-7.
18. Raza K, Talwar V, Setia A, Katare OP. Acne: An understanding of the disease and its impact on life. Int J Drug Dev Res 2012;4:14-20.
19. Lolis MS, Bowe WP, Shalita AR. Acne and systemic disease. Med Clin North Am 2009;93:1161-81.
20. Bhambri S, Del Rosso JQ, Bhambri A. Pathogenesis of acne vulgaris: Recent advances. J Drugs Dermatol 2009;8:615-8.
21. Zouboulis CC, Degitz K. Androgen action on human skin – From basic research to clinical significance. Exp Dermatol 2004;13 Suppl 4:5-10.
22. Leowattana W. DHEAS as a new diagnostic tool. Clin Chim Acta 2004;341:1-5.
23. Saleh BO. Role of growth hormone and insulin-like growth factor-I in

hyperandrogenism and the severity of acne vulgaris in young males. Saudi Med J 2012;33:1196-200.
24. Makrantonaki E, Ganceviciene R, Zouboulis C. An update on the role of the sebaceous gland in the pathogenesis of acne. Dermatoendocrinol 2011;3:41-9.
25. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, Xia L, *et al.* New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol 2009;18:821-32.
26. Layton AM. Disorders of the sebaceous glands. In: Burns DA, Breathnach S, Cox N, Griffiths C, editors. Rook's Textbook of Dermatology. 8th ed. London: Willey-Blackwell; 2010. p. 1-82.
27. Tahir CM. Pathogenesis of acne vulgaris: Simplified. J Pak Assoc Derma 2010;20:93-7.
28. Durdiakova J, Ostatnikova D, Celec P. Testosterone and its metabolites – Modulators of brain functions. Acta Neurobiol Exp (Wars) 2011;71:434-54.
29. van Anders SM, Goldey KL, Bell SN. Measurement of testosterone in human sexuality research: Methodological considerations. Arch Sex Behav 2014;43:231-50.
30. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. J Clin Endocrinol Metab 2009;94:907-13.
31. Miranti U, Indramaya DM, Sukanto H. Association of Serum Testosterone with Various Severity of Acne Vulgaris in Adult Women. Berkala Ilmu Kesehatan Kulit Kelamin 2017;29:98-105.