



RESEARCH ARTICLE

REVISED Assessment of serum testosterone, estradiol, and progesterone levels in female patients with acne vulgaris

[version 4; peer review: 1 approved, 2 not approved]

Previously titled: Assessment of serum hormone levels in female patients with acne vulgaris

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Abstract

Introduction: Acne is a chronic inflammatory disorder of the pilosebaceous unit with differential pathogenesis. To elucidate the roles of hormones in acne pathogenesis, we conducted a study to evaluate the serum testosterone, estradiol, and progesterone levels in women with acne vulgaris.

Methods: We conducted a cross-sectional descriptive study, and 175 women with acne vulgaris were examined; their serum estradiol, progesterone, and testosterone were analyzed by chemiluminescence technique and compared with the healthy control group.

Results: Increased serum hormone levels in women with acne vulgaris accounted for 29.7%, and hyperandrogenism accounted for 16.0% of cases. We found significant differences in testosterone levels (mean value, 55.67±25.56 versus 38.37±10.16 ng/dL, p<0.05) respectively, in the acne group and the control group. However, the estradiol level of the acne group (323.15±93.31 pmol/L) was lower than the control group (370.94±58.88 pmol/L), with p-value under 0.05. No statistically significant differences were found for progesterone (0.60±0.38 versus 0.50±0.15 ng/mL, p>0.05) levels. Moreover, we did not find the relationship between serum hormone levels and the severity of acne vulgaris.

Conclusion: This study showed that female acne vulgaris patients may have high serum testosterone levels and low serum estradiol

Open Peer Review

Approval Status   

	1	2	3
version 4 (revision) 22 Apr 2022			 view
version 3 (revision) 04 Apr 2022			
version 2 (revision) 09 Feb 2022	 view	 view	
version 1 11 Jan 2022	  view		

- Berna Aksoy**, Bahcesehir University, Istanbul, Turkey
- Jerry Tan** , University of Western Ontario, London, Canada
- Mohamed Badawy Hassan Tawfik Abdel-Naser**, Bawabet Al Hayah Medical Center,

levels compared with those of female controls. However, hormone alterations had no correlation with acne severity.

Keywords

Acne vulgaris, hormone

Cairo, Egypt

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Nguyen PC:** Data Curation, Formal Analysis, Investigation, Software, Writing – Review & Editing; **Nguyen HV:** Data Curation, Investigation, Writing – Original Draft Preparation; **Vu VT:** Data Curation, Investigation, Visualization, Writing – Original Draft Preparation; **Pham VT:** Data Curation, Methodology, Resources, Supervision; **Tran DQ:** Project Administration, Resources, Supervision, Visualization; **Nguyen TT:** Investigation, Supervision, Visualization

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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REVISED Amendments from Version 3

In the new version, we added detailed information about the included criteria. We also described the protocol of endocrine evaluation. And we put notes of abbreviations at the bottom of each table.

Any further responses from the reviewers can be found at the end of the article

Introduction

Acne is a chronic inflammatory disorder of the pilosebaceous unit with various manifestations, including non-inflammation and inflammation lesions. Collier *et al.* (2008) investigated 1013 Americans aged 20 years and older; 73.3% (744) reported ever having acne, and more women suffer from acne than men.¹ Four major factors involved in acne pathogenesis are excessive sebum production, follicular hyperkeratinization, hyper-colonization of the duct by *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and the production of inflammation.² Moreover, the hormone plays a part role in the pathogenesis of acne. Some studies found that acne had a relationship with hyperandrogenemia in female patients.³ Estradiol, the primary female sex hormone known as the major active estrogen, forms in absolute serum levels and estrogenic activity during human female reproductive years. Supplying sufficient amounts of estrogens will decrease sebum production and may act by suppressing androgen production by inhibiting the pituitary from secreting gonadotropin.⁴ The effect of progesterone on sebaceous glands was still disputed. Some authors have blamed progesterone for the change in sebum production in females during the menstrual cycle. However, this theory has not been proved experimentally.⁵ Therefore, we conducted this study to evaluate the serum testosterone, estradiol, and progesterone levels and the correlation of hormonal alterations with the severity of acne in women with acne vulgaris.

Materials and methods

The cross-sectional study was conducted on 175 female patients diagnosed with acne vulgaris and 35 age-matched healthy females. Patients were recruited from the clinic of the Dermatology department, 103 military hospital, Vietnam, from January to October 2019. Approval was obtained from the ethics committee of the Hanoi Department of Science and Technology. Written informed consent for publication of the patients' details was obtained from the patients.

We selected female acne patients aged between 16 and 25 who had not received drugs causing acne (glucocorticoids, lithium, isoniazid, phenytoin, selective reuptake serotonin inhibitors) or hormonal therapy (hormonal contraceptive and anti-androgen therapy) for at least three months before joining the study. Age-matched healthy volunteers without acne, pregnancy, or lactation served as the control group. None of the participants had been treated with hormonal treatment at this time of the study. All patients of each group were asked about history taken, throughout local and general clinical examinations to rule out any suspected similar diagnosis or other local and systemic disorders which contraindicate the patients from participating in this study. PCOS was also excluded by the manifestation of hyperandrogenism (hirsutism, oligomenorrhea) and confirmed with transvaginal and pelvic ultrasound.

Acne severity grading: The severity of acne was determined according to the Global Acne Grading System (GAGS).⁶ Each type of acneiform lesion has a gravity score: no lesions: 0; comedones: 1; papules: 2; pustules: 3; and nodules: 4. The local score was calculated using factor \times grade 0-4. Depending on the acne lesion location, the factor had the following values: forehead: 2; right cheek: 2; left cheek: 2; chin: 1; thorax and upper torso: 1. The sum of the local scores was the global score which settled acne severity. In our study, a global score of 1-18 signified mild acne, 19-30 was moderate acne, and a global score > 31 was severe acne.

Endocrine evaluation: Each patient performed a hormonal profile, including testosterone, estradiol, and progesterone. Blood samples were collected at 08:00 am on the second to the fourth day of menses (the follicular phase of the menstrual cycle). Each 4 mL of venous blood was centrifuged and serum stored at -20°C . Hormone levels were measured by using direct chemiluminescent technology in the Unicel[®] DXI800 machine. Units: testosterone for ng/dL, estradiol for pmol/L, progesterone for ng/mL. Women's testosterone normal levels were considered as ≤ 0.86 ng/mL; estradiol ranged from 74-532 pmol/L; progesterone was ≤ 1 ng/mL.

Data analysis

The data were analyzed by SPSS software version 22.0. Mean SD is in the form: $\bar{X} \pm \text{SD}$, comparing two means using the student t-test. The research results were compared by the Chi-squared test. P values of less than 0.05 were considered to be significant.

Results

Two hundred and ten female participants were enrolled in the study and divided into 175 female patients with acne vulgaris and 35 healthy controls. The mean age of patients for the acne group was 20.82 ± 2.53 years, and for the controls, it was 19.91 ± 2.57 years ranging from 18 to 25 years (Table 1).

The serum hormone levels between both groups are shown in Table 2. The plasma testosterone level of the acne vulgaris patients was significantly higher than the control group (55.67 ± 25.56 ng/dL, 38.37 ± 10.16 ng/dL, respectively). On the other hand, plasma estradiol level in acne vulgaris patients was lower than in the control group ($p < 0.05$). However, plasma progesterone levels were not different between both groups.

Regarding the hormonal alteration proportion, fifty-two patients (29.7%) out of 175 acne patients had hormonal alterations, including 28 patients (16%) with hyperandrogenism; 20 patients (11.43%) had increased serum progesterone levels, only four patients (2.29%) had increased serum estradiol level, and no patient had low hormonal levels as shown in Table 3.

Table 1. Age and BMI features of acne vulgaris group and control group.

Characteristics	Acne group (n=175)	Control group (n=35)	p-value	Normal range
Average age (years)	20.82 ± 2.53	19.91 ± 2.57	>0.05	
BMI (kg/m ²)	19.33 ± 1.51	18.90 ± 1.62	>0.05	18.5–24.9

BMI, body mass index.

Table 2. Plasma hormone levels of acne vulgaris group and control group.

Characteristics	Acne group (n=175)	Control group (n=35)	p-value	Normal range
Testosterone (ng/dL)	55.67 ± 25.56	38.37 ± 10.16	<0.05*	6–86
Estradiol (pmol/L)	323.15 ± 93.31	370.94 ± 58.88	<0.05*	74–532
Progesterone (ng/mL)	0.60 ± 0.38	0.50 ± 0.15	>0.05	<1

*p-value<0.05 was considered statistically significant.

Table 3. Hormonal alterations in female acne patients.

Value	Testosterone	Estradiol	Progesterone	Total (n=175)
Normal	147 (84.0%)	171 (97.71%)	155 (88.57%)	124
Increase	28 (16.0%)	4 (2.29%)	20 (11.43%)	52 (29.7%)
Decrease	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 4. Plasma hormone levels in severity groups of acne patients.

Hormone	Acne vulgaris group			Control group (4)	p-value
	Mild (1)	Moderate (2)	Severe (3)		
Testosterone (ng/dL)	43.06 ± 14.76	56.92 ± 27.64	60.71 ± 25.85	38.37 ± 10.16	p _{1,4} >0.05 p _{2,4} <0.05* p _{3,4} <0.05*
	p>0.05				
Estradiol (pmol/L)	354.97 ± 108.46	325.13 ± 91.79	305.26 ± 83.0	370.94 ± 58.88	p _{1,4} >0.05 p _{2,4} <0.05* p _{3,4} <0.05*
	p>0.05				
Progesterone (ng/mL)	0.52 ± 0.32	0.59 ± 0.39	0.65 ± 0.40	0.50 ± 0.15	p _{1,4} >0.05 p _{2,4} >0.05 p _{3,4} <0.05*
	p>0.05				

*p-value<0.05 was considered statistically significant.

In terms of the relationship between serum hormone levels and acne severity, we found no different hormone levels between the grades of the acne vulgaris group. However, testosterone levels in moderate and severe groups were statistically significantly higher than in the control group. Estradiol levels in the moderate and severe groups were statistically significantly lower than in the controls ($p < 0.05$). Progesterone levels in the mild and moderate groups were similar to the control group, except in the severe group. These differences are shown in [Table 4](#).

Discussion

In this study, the median age in the acne groups was 20.82 ± 2.53 years, younger than the previous study, with a mean of 26.64 years.⁵

In literature reviews, authors conducted studies to determine the relationship between serum hormone levels and acne. However, the results were not consistent. In 2013, da Cunha *et al.* investigated 835 female patients with acne vulgaris and found that 56.52% of cases changed at least one androgen hormone, and DHEAS levels were the most frequently increased.⁵ In this study, we found that the rate of changing hormone levels in female patients with acne vulgaris was 29.14%.

Androgens play a crucial role in acne pathogenesis. Androgens increase sebum production and increase the keratinization process around the neck of hair follicles, facilitating the formation of acne. In the study by Cunha *et al.*, the authors found that the rate of androgenism was 10.77%.⁵ In 2014, Wei *et al.* found that serum testosterone levels were significantly increased in the acne patient group compared with controls.⁷ In this study, the testosterone level of the acne group was higher than controls, and the hyperandrogenism rate was 16%. This result was also consistent with the study by Bakry *et al.*² However, in the study by Cetinozman⁸ and Akdogan,⁹ no significant change in testosterone levels was found between the acne and control groups. The discrepancy among the research results can be explained that the numbers of samples of the previous authors were not large enough, and the method of grading the severity of acne disease between the studies was based on different scales. Furthermore, anti-androgen therapy improved acne lesions in patients with polycystic ovary syndrome,¹⁰ which shows the critical role of androgen in the pathogenesis of acne.

We hypothesize that estrogens might impact sebum secretion by three different mechanisms: the opposition of androgens within the sebaceous glands, inhibition of gonadal androgen production *via* a negative feedback mechanism on gonadotropin release, and affects genes that play a role in sebaceous gland growth and lipid production.¹¹ Wei *et al.* surveyed 118 female acne patients compared with 90 sex-matched controls. The results showed that the estradiol level in the acne group decreased significantly compared with the control group.⁷ This result was also consistent with our result.

Testosterone is converted into a more potent form DHT by 5-ARD (5 α -reductase) enzyme causing an excess sebum production, whereas progesterone inhibits the activity of this enzyme and prevents turning testosterone into DHT. So, progesterone itself might be expected to reduce sebaceous gland activity. However, the progesterone effect on acne remains unclear. Although some studies show that progesterone can reduce androgen effects by inhibiting the 5-ARD enzyme or androgen receptors,¹² the fluctuation of sebum production in women during the menstrual cycle and premenstrual cyclic flare has partly been associated with progesterone, and some progestins lead to an exacerbation of acne by interacting with androgen receptors.^{12,13} In our study, there was no statically significant difference between the acne group and controls in terms of serum progesterone levels. However, the progesterone level of the severe acne was higher than the control group. In the study by Bakry *et al.*, the progesterone levels in female acne patients were higher than those in the control group.² It was similar to the study by Arora *et al.*¹⁴ The difference in results between our study and other studies can be explained by the different days of hormone tests in the menstrual cycle and different inclusion criteria. Arora¹⁴ and Bakry² investigated plasma hormones during the luteal phase of menses. Meanwhile, we performed in the follicular phase of menses.

There was no significant correlation of testosterone, estradiol, and progesterone levels with severity with Spearman Correlation ([Table 4](#)). In the study by Kiaynai *et al.*, there was no positive correlation between testosterone plasma levels and the severity of acne.¹⁵ Skrgatic *et al.* reported similar results when investigating Croatian females of reproductive age.¹⁶ In contrast, Rehman *et al.* found a correlation between acne severity and plasma testosterone levels.¹⁷ However, these studies were based on small sample sizes and excluded patients with mild acne with no hyperandrogenism and selected patients with severe comedones, severe inflammatory and/or purulent papules, and mild acne patients with hyperandrogenism.

Conclusion

This study showed that female acne vulgaris patients might have high serum testosterone levels and low serum estradiol levels compared with those of female controls. However, hormone levels differences had no correlation with acne grade.

Data availability

Underlying data

Dryad: Underlying data for 'Assessment of serum hormone levels in female patients with acne vulgaris'. <https://doi.org/10.5061/dryad.bvq83bk9z>¹⁸

The project contains the following underlying data:

- DATA.xlsx

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

Ethics approval

Approval was obtained from the ethics committee of Hanoi Department of Science and Technology with the code: 01C-08/14-2017-3. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate

Written informed consent for publication of the patients' details was obtained from the patients.

Acknowledgments

The authors would like to thank the Department of Dermatology and Venereology of 103 Military hospital, Military Medical University, for their support during the study and the patients for their voluntary participation in this research.

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Open Peer Review

Current Peer Review Status:   

Version 4

Reviewer Report 28 October 2022

<https://doi.org/10.5256/f1000research.130606.r152628>

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 **Mohamed Badawy Hassan Tawfik Abdel-Naser**
Bawabet Al Hayah Medical Center, Cairo, Egypt

The authors stated that the acne group and the normal control are age-matched. You may kindly avoid this term, because they are not matched.

In the title, abstract and material and methods, the authors used the term "serum"; most importantly they collected sera, whereas in the table and also in the text they used the term "plasma". What is the reason for this?

In general, several researchers do not recommend assessment of androgens, LH, etc., in acne patients because of the hormonal circadian fluctuation unless there is clinical evidence of hormonal disturbance. There are also several confounding variables. This may provide an explanation for the inconsistent results of hormonal assessment studies that the authors of the present study referred to.¹

Another explanation for the inconsistent results is inadequate study design. In the present study authors assessed serum testosterone, estradiol and progesterone in females with acne vulgaris (n=175). Hormones levels were compared with the healthy control (n=35) of similar age. Students' test is used for the comparisons. Clearly, the control group is inadequate as it has an unacceptable large margin of error (roughly $1/\sqrt{35} = 17\%$). On the other hand, the test group has less margin of error but still large (roughly $1/\sqrt{175} = 7.5\%$). Accordingly, unpaired t test may return erroneous/misleading results. In addition, and considering estradiol as an example, its reference range is 74–532 pmol/L, in the test group the mean \pm SD is 323.15 ± 93.31 and in the healthy control the mean \pm SD is 370.94 ± 58.88 . Ninety five percent (95%) of the healthy normal population will have estradiol levels in the range of 74-532 pmol/L as previously mentioned. By analogy and in this study, 95% (mean \pm 2 SD) of females with acne have estradiol levels in the range of 136.53 – 509.78 and the healthy control group in the range of 253.15-488.7. Note that these ranges in both acne group and control group are within the normal reference range, i.e., they are normal. Accordingly, the mentioned statistical significance ($p < 0.05$) is of no particular scientific (medical) relevance. The same concept (analysis) can also be applied on all assessed hormones.

The authors stated that 16% (n=28) of females with acne have increased testosterone level but no symptoms or signs of virilism. Was this increase above the upper limit of the lab reference range (6-86 ng/ml) or in comparison with the control group (n=35)?. This is again of no particular relevance not only because the control group is inadequate but also due to possible confounding factors. Based on the aforementioned arguments the provided statistical evaluation is misleading. There are several other similar but complex issues regarding the study design.

Some of the terms, phrases and sentences are not easy to comprehend.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Acne, pigmentary disorders

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Version 2

Reviewer Report 08 March 2022

<https://doi.org/10.5256/f1000research.121108.r126046>

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✘ **Jerry Tan** 

Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada

Most importantly, there is inadequate detail on the acne and control cohorts. In the former, it is important to ensure selection criteria are detailed as it is not stated. How will the reader know that these patients were not pre-selected based on a history or physical findings of virilism or other hyper-androgenic features? In the latter, most significant are age matching and ensuring that controls were not on birth control pills or other hormonal therapies that may confound hormonal test results.

Secondly, determination of acne severity uses a scale not typical for clinical or epidemiological acne research.

Furthermore, there are prior studies showing no association between hormonal abnormalities and acne in women – these should be referenced.

Finally, there is awkward sentence structure, syntax and word choice leading to difficulty in my comprehension.

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Acne

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 30 Mar 2022

NGUYEN CUONG, Vietnam Military Medical University, HaNoi, Vietnam

- We added the inclusion and exclusion criteria in detail for the control and acne groups in the new version of our article.
- In the previous article, we based on the acne grading score by Karen Mckoy. This score was not used widely in other studies, and we adjusted and fixed them suitable with the Global Acne Grading System. In our research, a global score of 1-18 signified mild acne, 19-30 was moderate acne, and a global score > 31 was severe acne.
- Some authors found no relationship between hormone disorders and acne in female patients in the literature. And we added the results of these studies and gave our discussion about this difference.

Competing Interests: No competing interests were disclosed.

Reviewer Report 16 February 2022

<https://doi.org/10.5256/f1000research.121108.r122986>

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Berna Aksoy

Department of Dermatology, Faculty of Medicine, Bahcesehir University, Istanbul, Turkey

The article is satisfactory in its revised form: approved.

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 02 February 2022

<https://doi.org/10.5256/f1000research.79509.r119712>

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Berna Aksoy

Department of Dermatology, Faculty of Medicine, Bahcesehir University, Istanbul, Turkey

This manuscript evaluates serum hormone levels in women, comparing with a control group. The manuscript evaluated 3 hormones at menstruation period. However, the manuscript needs revision as:

Progesterone 0,5 vs 0,6 may be better analysed by increasing control size, which is too small (175 vs 35). Additionally severe acne vs control group progesterone levels are significantly different. For a better statistical analysis the control group should be nearly half, and I think, therefore, that increasing control size will be meaningful statistically. The same is applicable to progesterone levels.

Acne vulgaris is a term up to age 25, what is the rationale that you choose 30 years? Acne adultorum is supposed to be related to hormonal disturbances. Many acne adultorum patients are stressful working women, there is an increased rate of stress hormones such as prolactin and cortisol. It is better you exclude women over 25.

Estradiol, progesterone and testosterone levels are in fact not enough for hormonal evaluation in women.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Acne

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 07 Feb 2022

NGUYEN CUONG, Vietnam Military Medical University, HaNoi, Vietnam

1. Progesterone 0,5 vs 0,6 may be better analysed by increasing control size, which is too small (175 vs 35). Additionally severe acne vs control group progesterone levels are significantly different. For a better statistical analysis the control group should be nearly half, and I think, therefore, that increasing control size will be meaningful statistically. The same is applicable to progesterone levels.

- This article studied the relationship between acne vulgaris with three degrees of disease and hormone levels. And mild acne was found not in relation to sex hormone disorders. This study tried to find this relationship in the moderate and severe groups, with 35 patients in each group. So we decided to choose the control group of around 35 patients. To be more meaningful statistically, we will increase the number of patients in the control group.

2. Acne vulgaris is a term up to age 25, what is the rationale that you choose 30 years? Acne adultorum is supposed to be related to hormonal disturbances. Many acne adultorum patients are stressful working women, there is an increased rate of stress hormones such as prolactin and cortisol. It is better you exclude women over 25.

Acne that occurs in patients over 25 years old is called post-adolescent acne, and the

hormone levels in these patients will be affected by external factors such as stress. And Our study first chooses female acne patients ranging from 16 to 30. When we checked our data and found that patients over 25 years old had no change in my statistical data, we could replace the inclusive criteria field that we chose the patients from 16 to 25 years old.

3. Estradiol, progesterone, and testosterone levels are in fact not enough for hormonal evaluation in women.

- Thank you for your comment. We will consider changing the article to "Assessment of serum testosterone, estradiol, and progesterone levels in female patients with acne".

Competing Interests: Author

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