Egyptian Journal of Medical Research

Print ISSN: 2682-4396 / Online ISSN: 2682-440X

Measurment of Serum level of Catestatin in patients with Acne vulgaris

Hanan Abdelrazik kamel [1], Hoda Ramadan Reyad[2], Omniya Badr Salah Khattab[3], Rehab Mohamed Naguib[1]

[1]*Dermatology department, Faculty of Medicine, Beni-Suef University, Beni-Suef 62511, Egypt*

[2]*Biochemistry department, Faculty of Medicine, Beni-Suef University, Beni-Suef 62511, Egypt*

[3]*Dermatology department, Sheikh Zayed Specialized Hospital, Giza12511, Egypt*

Article Info

Corresponding Author:
Omniya Badr Salah Khattab
omniyabadr28@gmail.com

Keywords
Acne vulgaris
catestatin
severity

Abstract

Background: Acne is a persistent inflammatory condition of the pilosebaceous unit. The pathogenesis encompasses three components: hyperseborrhea, aberrant follicular keratinization, and the development of Propionibacterium acnes inside the pilosebaceous unit. **Objective:** To evaluate serum catestatin (CST) level in Acne vulgaris patients as an attempt to answer the question about its role in disease pathogenesis and severity. **Patients and Methods:** This case-control study was carried out on 45 patients with different degrees of acne vulgaris severity (Group A) in addition to 45 age and sex matched healthy volunteers as a control group (Group B). For all participants, thorough history taking and good general and dermatological examination were done. Serum levels of catestatin were tested. **Results:** The present investigation revealed that

CST levels (ng/ml) in acne vulgaris patients were reported at (8.21±5.70 ng/ml), but in healthy controls, they were (3.04±0.84 ng/ml). A very substantial difference existed between the two groups. Serum levels of CST were somewhat elevated in females relative to men; however, this disparity was statistically insignificant. The levels of CST were elevated in individuals with severe lesions; nevertheless, the serum levels of CST exhibited a non-statistically significant difference concerning lesion severity. There was a significant negative correlation between CST level (ng/ml) and age (years) of the acne patients (r=-0.321, p=0.032). **Conclusion:** A very substantial difference existed between the two groups regarding CST level but connection to acne severity was not verified.

1. Introduction:

Persistent inflammation of the sebaceous glands causes acne. Despite its occasional appearance in adults, acne typically manifests during adolescence. Hyperseborrhea, abnormal follicular keratinization, and the growth of Propionibacterium acnes inside the pilosebaceous unit are the three parts that make up the disease. When they interact, they alter the epidermal microenvironment, triggering an inflammatory response in the host that accelerates the development of acne lesions **[1]**. It affects around 9.4 percent of the world's population, with the highest prevalence among adolescents. It affects more than 80% of women and 90% of men of all racial and ethnic backgrounds. According to **Alanazi et al. [2]**, there is a significant ethnic and national disparity in the prevalence of acne among adults and adolescents. Mild to moderately severe inflammatory lesions, papules, and pustules, sometimes accompanied by a small number of closed comedones or microcysts, characterize the condition. According to **Bagatin et al. [3]**, hyperpigmentation that occurs after an inflammation is common.

The diet has gotten a lot of attention in the etiology field because it is strongly linked to certain biochemical markers and the expression of genes that control sebaceous gland function, inflammation, and bacterial growth **[4]**. Clinical evidence suggests that acne is more common in the kids of acne-prone parents. In severe acne, when nodules, cysts, and scarring are present, heredity has a far larger role in how the condition presents. Acne risk was positively associated with being overweight or obese. On the other hand, various studies discovered an inverse relationship between the number of lesions and body mass index (BMI) in women with moderate to severe post-adolescent acne in the 25–45 age group. According to a nationwide study of 600,404 teens, there is a dose-dependent negative connection between being overweight or obese and acne **[5].**

Recent research has demonstrated the antibacterial properties of catestatin, a neuroendocrine peptide, on the skin. It influences human autonomic function. A total of three SNPs—Gly364Ser, Pro370Leu, and Arg374Gln—affect human catestatin. **Aung et al. [6]** found that neuropeptides and antimicrobial peptides both activate mast cells.

A key component of the skin's innate and adaptive immune systems is the production of antimicrobial peptides (AMPs). **Aung et al. [6]** discovered that AMPs from the skin, like human β-defensins and LL-37, have many immunomodulatory effects on different types of cells and can also kill microbes. A number of AMPs are part of the host's innate immune system, which provides cellular and molecular defense against pathogens. Catestatin was very effective at killing a number of different skin microorganisms. Catestatin has a pivotal role in regulating lipid metabolism and so reducing the risk of obesity **[7]**. This research sought to quantify serum catestain levels in individuals with acne vulgaris and examine its correlation with disease severity to evaluate its function in the pathophysiology of acne vulgaris.

2. Patients and methods:

2.1. Study design:

This study is a case-control was carried out at Dermatology outpatient clinic at Beni-Suef University hospital from July 2023 to December 2023 on acne patients attending Beni-Suef University hospital.

2.2. Sample size calculation:

The sample size was calculated using G* power (Faul et al, 2007) statistical software for sample size calculation; a number of 90 patients should be

enrolled in the trial with an allocation rate 1:1, power of the study 80%, confidence level 95%, and effect size 0.6.

2.3. Study participants:

2.3.1. Ninety participants were divided into two groups:

• Group A: Consisting of 45 individuals diagnosed with Acne vulgaris. The confirmation of acne vulgaris diagnosis was relied on the characteristic clinical presentation associated with this condition.

• Group B: Consisting of 45 individuals who appeared healthy and were matched for age and sex, serving as controls, with no personal or family history of acne vulgaris.

2.3.2. Patients and controls were selected according to the following inclusion and exclusion criteria:

- Inclusion criteria:

- Patients not receiving acne vulgaris systemic nor topical treatment.
- Both males and females will be included.

- Exclusion criteria:

- Age below 20 and above 50.
- Patients receiving acne vulgaris treatment in the last three months.
- Patients with other autoimmune diseases.
- Patients with associated systemic or dermatological diseases controls randomly from any other outpatient clinic.

2.4. Methods:

All participants were subjected to the following:

2.4.1. Full history taking:

- Name, age, sex, marital status, residence, special habits of medical importance.
- Onset, course, and duration of the disease (in the patients' group).
- Consanguinity and similar condition within family members.

2.4.2. Full clinical examination:

- Complete general examination.
- Complete cutaneous examination to evaluate the severity of acne; mild, moderate and severe.

2.4.3. Measurement of catestatin levels:

We used R&D Systems' ELISA kits of human catestatin to determine the catestatin concentrations following manufacturer instructions.

2.5. Statistical Analysis:

Collecting and analyzing data using SPSS version 25 for Windows 10 was the process. We used these tests: Chi Square test ($\chi 2$), student t-test, One-way ANOVA test and Pearson's correlation study examined the linear association between CST levels and other parameters in Acne patients' serum.

Correlation graphs deemed significant at P < 0.05. Correlation is positive (direct correlation) when r (correlation coefficient) is positive and negative (inverse correlation) when r is negative. Weak correlation is defined as r = >0 - 0.35, moderate correlation as r = >0.35 - 0.65, and strong correlation as r > 0.65. Statistics were deemed significant if P-values were 0.05 or below.

2.6. Ethical Considerations:

The ethical committee of the Faculty of Medicine, Beni-Suef University, granted approval for the study. Approval Number: FMBSUREC/09072023/Khattab. All participants provided informed written consent prior to their recruitment in the study, following a thorough explanation of the study's objectives. The handling of the database ensured confidentiality was maintained. All participants in the study were made aware of the procedures involved and were informed of their rights to decline participation or withdraw from the study at any time without needing to provide justification

.

3. Results:

In Table (1): 60% of Acne Vulgaris patients were females and 40% were males. There was no statistically significant difference between Acne and control groups regarding sex (p=0.368).

Table (1): Sex Distribution of the Studied Population (N= 90)

				TOTAL	**p-value**
		Acne Cases N= 45	**Healthy Controls N= 45**		
Sex (n, %)	**Male**	18 (40%)	25 (55.6%)	43 (47.8%)	0.368 (NS)
	Female	27 (60%)	20 (44.4%)	47 (52.2%)	

* P-value ≤ 0.05 is considered significant by (Chi-Square test).

In table (2): There was no statistically significant difference between cases and control groups regarding age (p=0.342).

Table (2): Age Distribution of the Studied Population.

	20-25 y	**26-30 y**	**30-40 y**	**p-value**
Acne Cases (N)	24	12	9	0.342
Healthy Controls (N)	12	17	16	

* P-value ≤ 0.05 is considered significant by (Chi-Square test).

In table (3): (40%) of acne vulgaris group were severe, followed by mild lesions in (35.6%) of cases while, in 24.4% of acne cases the lesions were moderate. Acne vulgaris cases recorded (2.22±1.51) years suffering from the disease. The majority of the cases (55.60%) have regular menstrual cycle while only 4.4% of the patients have irregular cycle. 40% of the cases haven't been recorded.

Table (3): Severity, Duration of lesions, Menstrual cycle regularity in Acne Vulgaris patients (N= 45).

Severity of lesions N (%)	
Mild	16 (35.6%)
Moderate	11 (24.4 %)
Severe	18 (40.0%)
Duration (Years)	
Mean ±SD	2.22±1.51
Range	5.89
Minimum	0.11
Maximum	6.00
Variance	2.27
Menstrual cycle regularity	
Regular	25 (55.6%)
Irregular	2 (4.4%)
Not recorded	18 (40%)

Table (4) and figure (4) showed the descriptive statistics of catestatin levels (ng/ml) among both groups. Acne vulgaris cases recorded (8.21±5.70 ng/ml) while the levels in healthy controls were (3.04±0.84 ng/ml). There is a high significant difference (p<0.001) between both groups.

Table (4): Catestatin (ng/ml) levels among the studied groups

Catestatin (ng/ml) levels	Acne Cases (N= 45)	Healthy Controls (N= 45)	*p-value*
Mean ±SD	8.21±5.70	3.04±0.84	<0.001**
Standard error	0.85	0.12	
Range	17.9	4.60	
Minimum	1.30	0.20	
Maximum	19.20	4.80	

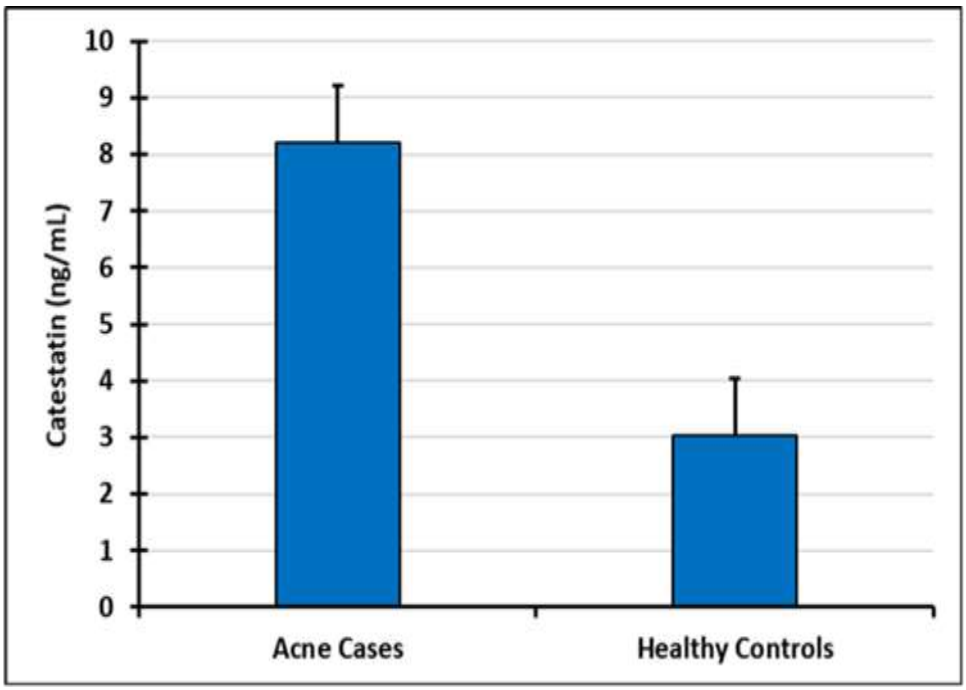

Figure (1): Catestatin levels among both groups

In table (5); serum levels of Catestatin were slightly higher among females as compared with males, however this difference was insignificant (p-values >0.05). Serum levels of Catestatin showed non-statistically significant difference in relation to severity of the lesions (p-values >0.05). However, it is clear that the levels of Catestatin were higher in patients with severe lesions (figure 2).

Table (5): Relation between Serum level of Catestatin with patients' gender and disease severity in studied acne patients; (N= 45):

			N	Mean	SD	Min.	Max.	p-value
Catestatin	**Sex**	**Male**	18	6.24	5.26	1.3	19.2	0.124 (NS)*
		Female	27	9.50	5.80	1.3	18.5	
	Acne Severity	**Mild severity**	16	7.76	5.13	1.30	19.20	0.07 (NS)**
		Moderate severity	11	5.54	4.82	1.30	15.50	
		Severe	18	10.55	6.22	2.40	18.20	

* P-value ≤ 0.05 is considered significant by (T-test).

** P-value ≤ 0.05 is considered significant by (one-way ANOVA).

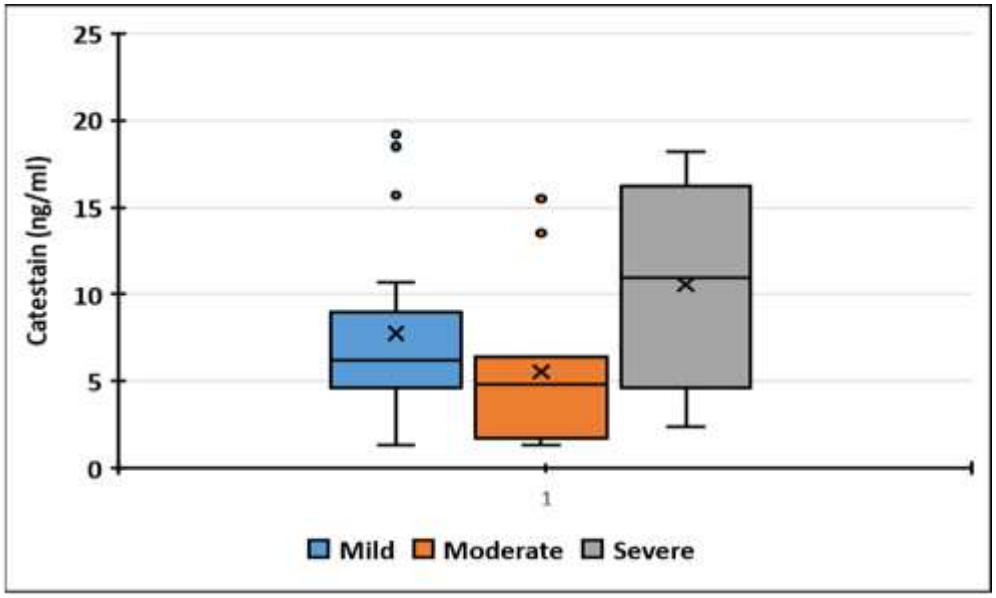

Figure (2): Catestatin levels in relation to Acne Severity

In table (6): showed the correlations between Catestatin level (ng/ml) and age (years) of the acne patients. There is a significant negative correlation recorded between them (figure 3) (r=-0.321, p=0.032). The correlations between Catestatin level (ng/ml) and disease duration (years) of the acne patients; There is no correlation recorded between them (r=-0.083, p=0.589)

Table (6): Correlation of serum level of Catestatin with some studied parameters in Acne group.

Variable	Catestatin	
	r	p-value
Age	-0.321	0.032*
Duration	-.083	0.589

r=Pearson's correlation coefficient

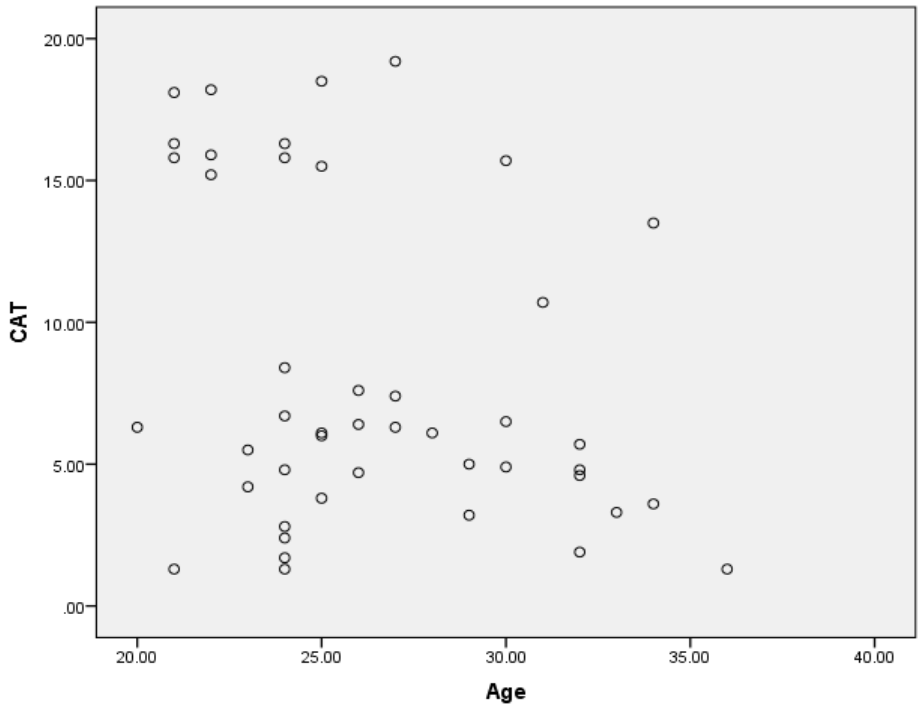

Figure (3): Correlation between serum level of Catestatin and age in Acne group.

4. Discussion:

Persistent inflammation of the sebaceous glands causes acne. Acne typically manifests during adolescence. Hyperseborrhea, abnormal follicular keratinization, and the growth of Propionibacterium acnes inside the pilosebaceous unit are the three parts that make up the disease. Acne lesions progress more rapidly when these factors combine, changing the epidermal microenvironment and triggering host inflammatory responses **[8]**.

Recent research has demonstrated the antibacterial properties of catestatin. Many different types of skin microbes were strongly killed by catestatin **[6, 7]**. The goals of this study are to determine the role of serum catestatin in the etiology of acne vulgaris and to

quantify serum catestatin levels in relation to acne vulgaris severity. In this study, researchers found that healthy controls had catestatin levels of 3.04±0.84 ng/ml, but acne vulgaris patients had values of 8.21±5.70 ng/ml. There was a huge disparity between the two sets of people. Although women had somewhat higher serum levels of Catestatin than men did, the difference was not statistically significant. Although there was an increase in Catestatin levels in patients with severe lesions, there was no statistically significant correlation between lesion severity and serum Catestatin levels.

Consistent with our findings, **Yücesoy et al. [9]** observed that serum catestatin levels were markedly elevated in patients with acne vulgaris when compared to healthy controls. The analysis revealed no significant difference in mean serum catestatin levels when comparing genders, with female patients showing levels of 0.42 ± 0.19 and male patients at 0.45 ± 0.21 ($p = 0.52$). Similarly, female controls had levels of 0.17 ± 0.03, while male controls were at 0.18 ± 0.01 ($p = 0.38$). An association appears to exist between the severity of acne vulgaris and serum catestatin levels, as patients with severe acne vulgaris exhibited significantly higher levels compared to those with mild and moderate cases.

Further investigation conducted by **Nagy et al. [10] and Nagy et al. [11]** revealed that P. acnes elevates levels of specific AMPs.

A neuropeptide, known as substance, P exhibits antimicrobial properties. The analysis revealed no statistically significant correlation between the concentration of substance P and acne severity; however, **Rokowska-Waluch et al. [12]** observed that individuals with acne exhibited a higher average serum level of this compound compared to the control group.

Findings from investigations conducted by **Ali et al. [13] and Nagiub et al. [14]** indicated that serum substance P levels are significantly elevated in individuals with acne vulgaris compared to control subjects.

El-Ramly et al. [15] observed that individuals with acne vulgaris exhibited notably elevated serum cathelicidin levels in comparison to the control group. Individuals experiencing severe acne exhibited the highest levels of serum cathelicidin; however, this variation did not reach statistical significance.

Al-Sudany et al. [16] discovered that serum koebnerisin levels in patients with acne vulgaris were significantly

elevated compared to those in the control group. In a similar vein, the levels of psoriasin and koebnerisin were significantly elevated in the skin of individuals with acne when compared to the control group, as reported by **Borovaya et al. [17].**

Chronnell et al. [18] observed that the acne vulgaris group exhibited significantly elevated levels of human β-defensin 1 and 2 in the sub-basal layer, outer hair follicles, and pilosebaceous ducts when compared to the control group. Acne vulgaris skin lesions also showed an enhanced HBD2 level, as pointed out by **Borovaya et al. [17]**.

AMPs directly kill a variety of bacteria, fungi, and enveloped viruses while also acting as an intrinsic chemical barrier for the epithelium. The innate immune system relies on these effector cells. In addition, when wounds are healing and when inflammatory and allergic diseases are present, their prevalence in the local tissues increases **[6]**.

As a chronic inflammatory disorder of the sebaceous glands, acne vulgaris affects a large percentage of the population. In acne vulgaris, AMPs serve as both a proinflammatory signaling molecule and a protective barrier against Propionibacterium acnes **[19]**.

Jati et al. [20] found that the antimicrobial peptide catestatin has several immunomodulatory properties. Yeast, fungus, bacteria, and other skin pathogens are all susceptible to catestatin's antimicrobial effects. PI3 kinase, nitric oxide, and MAPK-dependent pathways are just some of the signal transduction pathways that it turns on. It also attracts monocytes, which suggests that it may be involved in inflammation **[21]**. In addition, it helps keratinocytes move and makes IL-8, which suggests that it might play a role in immune regulation. Furthermore, catestatin may promote migration, degranulation, and the generation of chemokines and cytokines that promote inflammation in human mast cells **[19]**. When inflammation or sick tissues are present, inflammatory cytokines make it easier for immune cells to go to those locations. Because CST inhibits cytokine release, it lessens the likelihood of a post-implantation inflammatory reaction. We still do not fully understand the exact physiological effects of the CHGA-derived peptide, but what we do know strongly supports the pathophysiological function of CST in protecting the body from mechanical damage and inflammation **[7, 19]**.

These findings provide further evidence that increased inflammation and P. acnes colonization contribute to raised catestatin levels in acne vulgaris patients. The relationship between higher AMP levels and a more severe disease process remains unclear, as suggested by **Yücesoy et al. [9]**.

We studied several systemic chronic inflammatory illnesses by measuring serum catestatin levels. Rheumatoid arthritis (RA) patients had significantly higher serum Catestatin levels, according to **Simac et al. [22]**. New studies back up what was found in vitro about how CST affects intestinal flora. They show that people with inflammatory bowel disease (IBD) have much higher levels of CST in their blood. Catestatin may be involved in anti-inflammatory reactions and may be associated with an increased risk of cardiovascular disease in some people, according to the findings **[23, 24]**.

By reducing the formation of macrophages and the generation of proinflammatory cytokines (TNF-α, IL-1, and IL-6), catestatin reduces the inflammatory response **[22]**.

Acne patients' ages were negatively correlated with their Catestatin levels (ng/ml) in this study ($r = -0.321$, $p = 0.032$). As far as we are aware, no previous research has predicted a correlation between catestatin levels, acne and age. However, there is evidence that some chronic inflammatory illnesses are associated with elevated serum Catestatin (CST) levels.

Simac et al. [22] observed a significant correlation ($r = 0.418$, $p < 0.001$) between Catestatin levels and age in their examination of patients with rheumatoid arthritis. Patients undergoing hemodialysis with advanced chronic renal disease exhibited a strong positive correlation between age and Catestatin levels, as reported by Luketin et al. [25]. Earlier investigations indicated that the mean age of individuals with acne vulgaris was 56.1 ± 12.2 years according to Simac et al. [22], and 68.3 ± 12.6 years as reported by Luketin et al. [25]. This study specifically excluded individuals with systemic disorders, including cardiovascular disease and autoimmune illnesses, focusing instead on participants aged 20 to 40.

According to **Rabbi et al. [24]**, Catestatin may have a role in anti-inflammatory responses and an elevated risk of cardiovascular disease in individuals with rheumatoid arthritis and chronic renal impairment. While increased CST levels may suggest a

heavy burden of cardiovascular disease, aging affects the cardiovascular system, leading to an increased incidence of cardiovascular sickness **[26].**

The duration of acne in patients was found to be 2.22±1.51 years in this study, and there was no correlation between this duration and Catestatin levels (ng/ml) (r = -0.083, p = 0.589). We were unable to find any evidence in the literature that catestatin levels are associated with acne duration.

The duration of acne vulgaris varied from 18.08 to 23.623 months, according to **El-Ramly et al. [15]**. However, **El-Ramly et al. [15]** found no significant correlation between this duration and serum cathelicidin, an antimicrobial peptide.

While we found no correlation between serum Catestatin levels and the length of time a patient suffers from chronic inflammatory sickness, another study did identify such a correlation. Serum Catestatin levels were positively associated with rheumatoid arthritis (RA) duration, specifically with RA durations between 10 and 20 years, according to **Simac et al. [22]**.

CST modifies the balance between pro-inflammatory and anti-inflammatory cytokines via a range of signal transduction pathways that include both immune and non-immune cells. Furthermore, these results suggest that a more active disease activates regulatory mechanisms, resulting in the compensatory synthesis of CST, which safeguards the body against chronic inflammation. Furthermore, he discovered that CST can independently predict disease activity and functional impairment **[22]**.

5. Conclusions:

A significant disparity occurred between the two groups. Serum levels of CST were marginally increased in females compared to males; however, this difference was statistically insignificant. Serum CST levels did not change significantly by lesion severity, but they were higher in individuals with severe lesions. There was a strong negative correlation between the age (years) of acne patients and CST levels. CST levels were significantly different between the two groups, although there was no evidence that this difference was associated with more severe acne. On the other hand, more studies are needed to establish the utilization of AMPs in daily clinical practice.

6. References:

1. Dréno, B., Pécastaings, S., Corvec, S., Veraldi, S., Khammari, A., & Roques, C. (2018). Cutibacterium acnes (Propionibacterium acnes) and acne

vulgaris: a brief look at the latest updates. *Journal of the European Academy of Dermatology and Venereology*, *32*, 5-14.

2. Alanazi, M. S., Hammad, S. M., & Mohamed, A. E (2018): Prevalence and psychological impact of Acne vulgaris among female secondary school students in Arar city. Electronic physician.; 10(8): 7224–7229.
3. Bagatin, E., Freitas, T. H. P., Rivitti-Machado, M. C., Machado, M. C. R., Ribeiro, B. M., Nunes, S., & Rocha, M. A. D. D (2019): Adult female acne: a guide to clinical practice. Anais brasileiros de dermatologia.; 94(1): 62–75.
4. González-Mondragón, E. A., Ganoza-Granados, L. D. C., Toledo-Bahena, M. E., Valencia-Herrera, A. M., Duarte-Abdala, M. R., Camargo-Sánchez, K. A., & Mena-Cedillos, C. A. (2022). Acne and diet: a review of pathogenic mechanisms. Boletín médico del Hospital Infantil de México, 79(2), 83-90.
5. Yang, J., Yang, H., Xu, A., & He, L (2020): A Review of Advancement on Influencing Factors of Acne: An Emphasis on Environment Characteristics. Frontiers in public health.; 8, 450.
6. Aung, G., Niyonsaba, F., Ushio, H., Kajiwara, N., Saito, H., Ikeda, S., Ogawa, H., & Okumura, K (2011): Catestatin, a neuroendocrine antimicrobial peptide, induces human mast cell migration, degranulation and production of cytokines and chemokines. Immunology.; 132(4): 527– 539.
7. Deng, Z., & Xu, C (2017): Role of the neuroendocrine antimicrobial peptide catestatin in innate immunity and pain. Acta biochimica et biophysica Sinica.; 49(11): 967–972.
8. Dréno B (2017): what is new in the pathophysiology of acne, an overview. Journal of the European Academy of Dermatology and Venereology.; 31 Suppl 5, 8–12.
9. Ali Awad, E. Y., Soliman, F. E. S., & Maklad, S. A. (2022). The Effect of Acne Vulgaris on Body Image Satisfaction, Self Esteem and Quality of Life of Adolescents at Tanta city. *Tanta Scientific Nursing Journal*, *27*(4), 188-206.
10. El-Tahlawi, S. M., Mohamed, N. E., Mohamed, S. R., & Abd El Nasser, L. (2020). Serum level of vitamin D &Beta-2-defensin in patients with acne vulgaris. *Fayoum University Medical Journal*, *7*(1), 134-146.
11. Yücesoy, S. N., Ak, T., Öner, S., & Serdaroğlu, S. (2023). Serum

catestatin levels in patients with acne vulgaris: single-center prospective study. *Skin Appendage Disorders*, 1-7.

12. Durai, P. C. T., & Nair, D. G. (2015). Acne vulgaris and quality of life among young adults in South India. *Indian journal of dermatology*, *60*(1), 33-40.
13. George, R. M., & Sridharan, R. (2018). Factors aggravating or precipitating acne in Indian adults: a hospital-based study of 110 cases. *Indian journal of dermatology*, *63*(4), 328-331.
14. Jaber, R. M., Alnshash, B. M., Mousa, S. N., Fayoumi, H. S., Al-Qaderi, L. M., & Zant, A. M. (2020). The epidemiology of acne vulgaris among adolescents and young adults in Jordan University Hospital. *Open Journal of Nursing*, *10*(4), 353-366.
15. Shah, N., Shukla, R., Chaudhari, P., Patil, S., Patil, A., Nadkarni, N., & Goldust, M. (2021). Prevalence of acne vulgaris and its clinico-epidemiological pattern in adult patients: Results of a prospective, observational study. *Journal of cosmetic dermatology*, *20*(11), 3672-3678.
16. Skroza N, Tolino E, Mambrin A, Zuber S, Balduzzi V, Marchesiello A, Bernardini N, Proietti I and Potenza C (2018). Adult acne versus adolescent acne. J Clin Aesthet Dermatol. 11:21–25.
17. Al-Kubaisy, W., Abdullah, N. N., Kahn, S. M., & Zia, M. (2014). Sociodemographic characteristics of acne among university students in Damascus, Syria. *Epidemiology Research International*, *2014*(1), 974019.
18. Smithard, A., Glazebrook, C., & Williams, H. C. (2001). Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community-based study. *British Journal of Dermatology*, *145*(2), 274-279.
19. Ogé, L. K., Broussard, A., & Marshall, M. D. (2019). Acne vulgaris: diagnosis and treatment. *American family physician*, *100*(8), 475-484.
20. Özçelik, S., Kulaç, İ., Yazıcı, M., & Öcal, E. (2018). Distribution of childhood skin diseases according to age and gender, a single institution experience. Turkish Archives of Pediatrics/Türk Pediatri Arşivi, 53(2), 105.
21. Poli, F., Dreno, B., & Verschoore, M. (2001). An epidemiological study of acne in female adults: results of a survey conducted in France. Journal of the European Academy of

Dermatology and Venereology, 15(6), 541-545.

22. Nagy, I., Pivarcsi, A., Koreck, A., Széll, M., Urbán, E., & Kemény, L. (2005). Distinct strains of Propionibacterium acnes induce selective human β-defensin-2 and interleukin-8 expression in human keratinocytes through toll-like receptors. Journal of Investigative Dermatology, 124(5), 931-938.
23. Nagy, I., Pivarcsi, A., Kis, K., Koreck, A., Bodai, L., McDowell, A., ... & Kemény, L. (2006). Propionibacterium acnes and lipopolysaccharide induce the expression of antimicrobial peptides and proinflammatory cytokines/chemokines in human sebocytes. Microbes and infection, 8(8), 2195-2205.
24. Rokowska-Waluch, A., Pawlaczyk, M., Cybulski, M., Żurawski, J., Kaczmarek, M., Michalak, M., & Mojs, E. (2016). Stressful events and serum concentration of substance P in acne patients. *Annals of dermatology*, *28*(4), 464-469.
25. Nagiub, H., Elbayomi, Y., Mansour, M., & Zohdy, M. (2021). Serum level of the neuropeptide substance 'P'in patients with acne vulgaris. Egyptian Journal of Dermatology and Venerology, 41(1), 10.
26. El-Ramly, A. Z., Fawzi, M. M., Mahmoud, S. B., Ghaffar, M. M. A., & Shaker, O. G. (2016). Assessment of serum levels of cathelicidin and vitamin D in acne vulgaris. *Journal of the Egyptian Women's Dermatologic Society*, *13*(2), 99-105.
27. Al-Sudany, N. K., Mohammed, N. H., & Alrifai, S. B. (2019). Downregulation of S100a7a antimicrobial peptide in acne vulgaris patients after isotretinoin therapy. *Dermatologic Therapy*, *32*(6), e13136.
28. Borovaya, A., Dombrowski, Y., Zwicker, S., Olisova, O., Ruzicka, T., Wolf, R., ... & Sárdy, M. (2014). Isotretinoin therapy changes the expression of antimicrobial peptides in acne vulgaris. Archives of dermatological research, 306, 689-700.
29. Chronnell, C. M., Ghali, L. R., Quinn, A. G., Bull, J. J., McKay, I. A., Philpott, M. P., ... & Cunliffe, W. J. (2001). Human β defensin-1 and-2 expression in human pilosebaceous units: upregulation in acne vulgaris lesions. Journal of Investigative Dermatology, 117(5), 1120-1125.
30. Coates, S. J., Lee, E. H., & Granstein, R. D. (2017). Cutaneous Neuroimmunology. *Clinical and*

Basic Immunodermatology, 179-199.

31. Jati, S., Mahata, S., Das, S., Chatterjee, S., & Mahata, S. K. (2023). Catestatin: antimicrobial functions and potential therapeutics. *Pharmaceutics*, *15*(5), 1550.
32. Egger, M., Beer, A. G., Theurl, M., Schgoer, W., Hotter, B., Tatarczyk, T., ... & Kirchmair, R. (2008). Monocyte migration: a novel effect and signaling pathways of catestatin. European journal of pharmacology, 598(1-3), 104-111.
33. Simac, P., Perkovic, D., Bozic, I., Matijas, M., Gugo, K., Martinovic, D., & Bozic, J. (2022). Serum catestatin levels in patients with rheumatoid arthritis. Scientific Reports, 12(1), 3812.
34. Muntjewerff, E. M., Tang, K., Lutter, L., Christoffersson, G., Nicolasen, M. J., Gao, H., ... & Mahata, S. K. (2021). Chromogranin A regulates gut permeability via the antagonistic actions of its proteolytic peptides. Acta Physiologica, 232(2), e13655.
35. Rabbi, M. F., Munyaka, P. M., Eissa, N., Metz-Boutigue, M. H., Khafipour, E., & Ghia, J. E. (2017). Human catestatin alters gut microbiota composition in mice. *Frontiers in Microbiology*, *7*, 2151.
36. Luketin, M., Mizdrak, M., Boric-Skaro, D., Martinovic, D., Tokic, D., Vilovic, M., ... & Bozic, J. (2021). Plasma catestatin levels and advanced glycation end products in patients on hemodialysis. Biomolecules, 11(3), 456.
37. Ma, L. Y., Chen, W. W., Gao, R. L., Liu, L. S., Zhu, M. L., Wang, Y. J., ... & Hu, S. S. (2020). China cardiovascular diseases report 2018: an updated summary. Journal of geriatric cardiology: JGC, 17(1), 1.