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Interleukin-35 Level in Acne Vulgaris: A meta-analysis

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Abstract

Introduction: Interleukin-35 (IL-35) is an emerging biomarker at the forefront of research for diagnoses and treatments for acne vulgaris (AV). AV, commonly known as acne, is a skin disorder that affects millions of people across the globe. It is often seen in teens and young adults and is the most common skin disorder in the United States.

Aim of the study: To compare the outputs of different studies about IL-35 levels in AV patients as an anti-inflammatory cytokine.

Methods: This meta-analysis follows the PRISMA flow diagram and the guidelines of the Cochrane Handbook. We searched several electronic databases, such as the Web of Science, PubMed, Cochrane, and Scopus, from inception to April 2021 without any language restriction. We included patients with AV. Age: more than 18 and less than 35 years and both sex

Result: The present study showed that there was a highly statistically significant difference between patients and controls regarding IL-35 levels in serum and tissue. Results of the meta-analysis show that IL-35 levels in serum and tissues are significantly higher in the patients group compared with the control ($P < 0.001$). The pooled effect estimate revealed that there is significant difference between IL-35 levels in tissues according to grade of mild, moderate, and severe subgroups ($P < 0.001$)

Conclusion: Serum and tissue IL-35 were found to be major anti-inflammatory cytokines released by the sebaceous glands in our investigation. They were substantially more prevalent among acne patients. They were thought to play an important role in acne treatment at numerous points due to their anti-inflammatory properties. That could be hampered in AV by hitherto unknown impediments.

Keywords: acne vulgaris; cytokines, IL-35; anti-inflammatory.

1. Introduction

Interleukin-35 (IL-35) is an emerging biomarker at the forefront of research for diagnoses and treatments for acne vulgaris (AV). AV, commonly known

as acne, is a skin disorder that affects millions of people across the globe. It is often seen in teens and young adults and is the most common skin disorder in the

United States. Acne is characterized by clogged or blocked pores, whiteheads, blackheads, papules or pimples, cysts or nodules, and scars. It can be caused by a variety of contributing factors such as genetics, skin oil production, hormones, stress levels, and bacterial activity [1]. Treatment of AV can include medications like antibiotics or combination treatments (such as topical agents or oxidative agents), oral therapies including oral retinoids, hormonal treatments with oral contraceptives or spironolactone, chemical peels, and natural topical treatments like tea tree oil [2].

The importance of IL-35 in AV has only recently been explored in studies. IL-35 belongs to a cytokine family known as "interleukins", which are secreted proteins that act as messengers to coordinate immune responses between cells. Early research suggests that its role may extend beyond its ability to modulate inflammation in AV-

related diseases [3]. Specifically, it appears to potentially regulate sebaceous gland activity in treating AV patients. Higher levels of IL-35 have been linked to reduced acne flare-ups and improved healing effects from other topical treatments like tretinoin gel. Additionally, studies have demonstrated that patients with higher levels of IL-35 have increased sensitivity to UV radiation, suggesting reduced photodamage from sun exposure for AV-prone individuals [4]. Furthermore, IL-35 has been found to modulate growth factors necessary for host defense against microbial invasion, which could directly impact reducing inflammation associated with bacterial infections commonly associated with AV symptoms such as *P. acnes* colonization on the skin surface [5]. Thus, measuring the levels of this cytokine may provide further insight into the biology of AV, aiding in diagnoses and interventions specific to this inflammatory skin condition [6].

2. Methods

This meta-analysis followed the PRISMA flow diagram and the guidelines of the Cochrane Handbook.

2.1. Eligibility Criteria

Inclusion criteria include:

- Patients with AV.
- Age: more than 18 and less than 35 years.
- Sex: both sexes.

Exclusion criteria included:

- Patients who received any systemic and/or topical acne treatment in the last 3 months.

- Pregnant and lactating females.
- Patients with other dermatological diseases.
- Patients with any systemic illness, autoimmune diseases or infections.

2.2. Information Sources

We searched several electronic databases such as the Web of Science, PubMed, Cochrane, and Scopus from inception to April 2021 without any restriction to languages.

2.3. Search and Study Selection

The results of our search were exported to Endnote X8.0.1 which automatically removed any duplicated study. Then the results, after the removal of duplicates, were exported to Excel sheet 2016 version 2112 to perform a manual screening. Two independent investigators performed the manual screening in two steps. The initial phase was title and abstract screening, followed by full-text screening. The extraction of the data was performed in a standardized sheet including by two authors independently.

2.4.Data Collection

We collected data regarding the baseline demographics of included participants, outcome endpoints which included IL-35 in serum and tissues, and the data for risk of bias assessment. The process of data collection was done using Microsoft Excel.

2.5.Risk of bias Assessment

We used Cochrane's tool to assess the quality of the studies included [7]. This

evaluation comprised proper blinding, allocation concealment, and patient randomization throughout seven domains. Each domain may be a high, unclear, or low risk of bias.

2.6.Analysis

We used Review Manager Software to conduct the meta-analysis for this study. The results in our study were both continuous and dichotomous. All dichotomous data were analyzed using risk ratio (RR) and 95% CI. While the continuous data were analyzed using the mean difference. When the data were homogenous, the fixed-effects model was utilised, while heterogeneous data were examined using the random-effects model. We employed the I² and the p-value of the Chi-square tests to assess the occurrence of inconsistency among the studies. $P < 0.1$ or I² values of more than 50% were significant signs of heterogeneity. Using Cochrane's leave-one-out strategy, we attempted to resolve the inconsistency of varied results.

3. Results

The age and sex of the study groups are shown in Table 1.

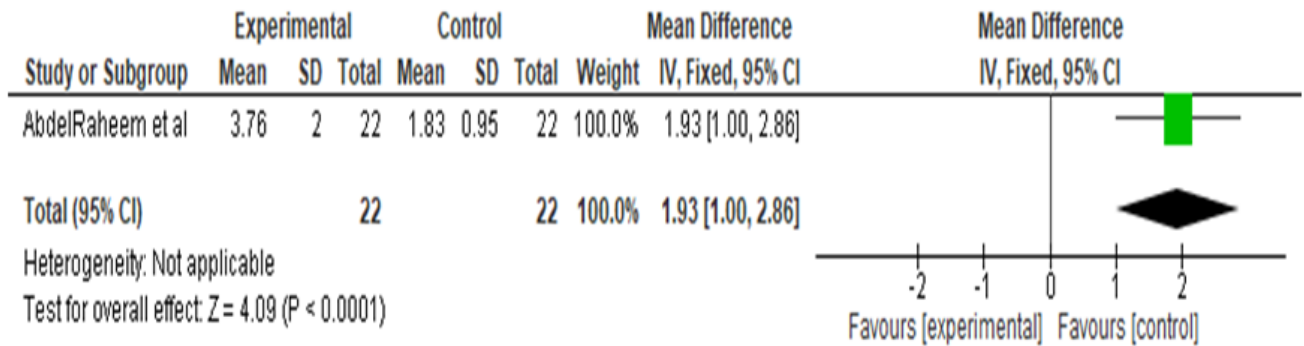
Table 1: Age and sex distribution among groups.

Variables	Groups	
	Patient (N=22)	Control (N=22)
Age (years)	22.32±4.77 (18-30)	24.27±4.59 (18-30)
Sex	Male	11 (50%)
	Female	11 (50%)

The present study showed that there was a highly statistically significant difference between patients and controls regarding IL-35 levels in serum and tissue.

Results of meta-analysis shows that IL-35 levels in serum and tissues are significantly higher in the patients group compared with control ($P < 0.001$) (Figure 1).

A)



B)

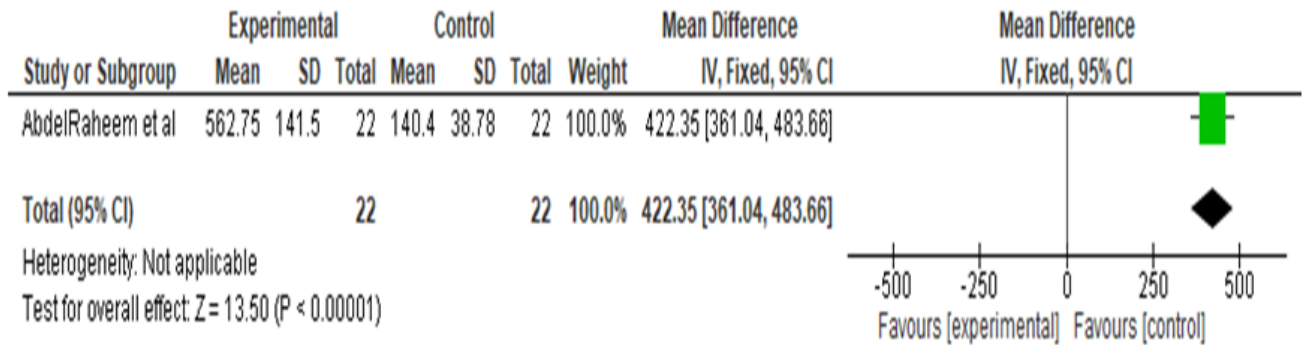
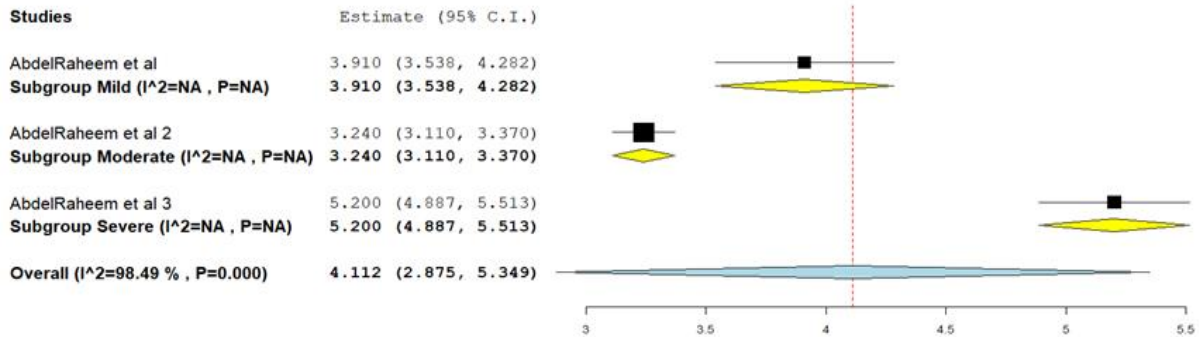


Figure 1: Meta-analysis of the IL-35 levels in A) serum and B) tissues.

The pooled effect estimate revealed that there is a significant difference between IL-35 levels in serum according to mild, moderate, and severe subgroups ($P < 0.001$) (Figure 2 A). The pooled effect estimate

revealed that there is a significant difference between IL-35 levels in tissues according to grade of mild, moderate, and severe subgroups ($P < 0.001$), (Figure 2B).

A)



B)

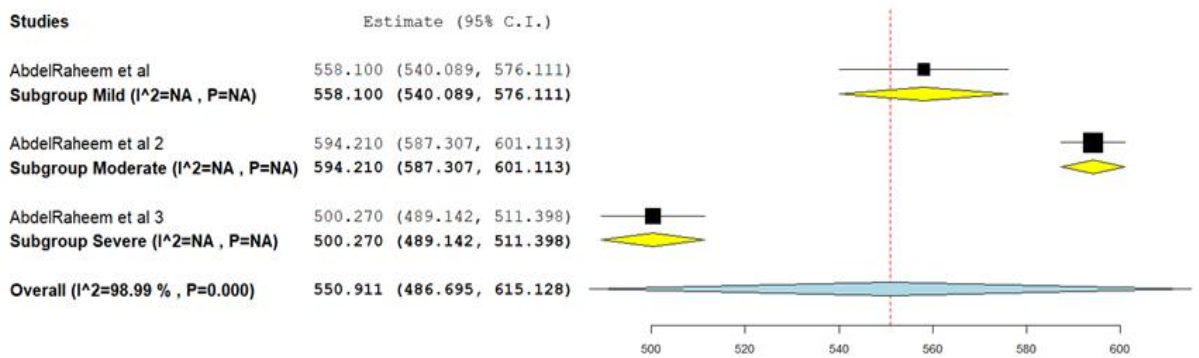
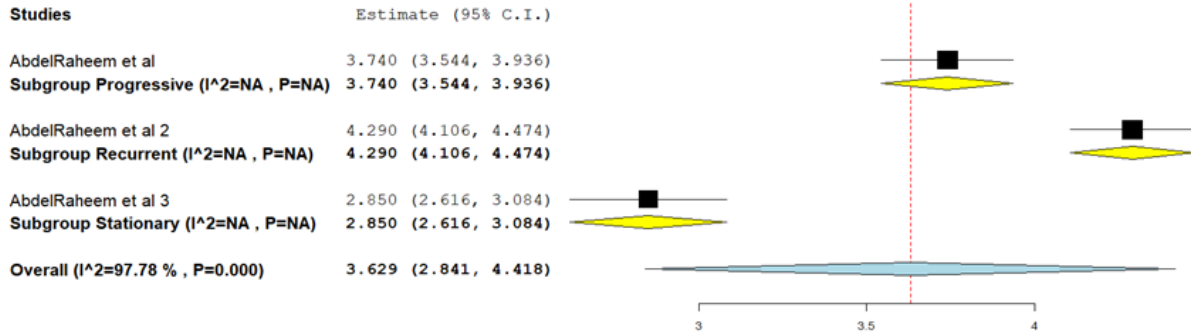


Figure 2: The pooled effect estimates of the IL-35 Grade in A) serum and B) tissues.

According to the course, the pooled effect estimate revealed that there was a significant difference between serum IL-35 levels in progressive, moderate, and severe subgroups ($P < 0.001$), (Figure 3A). For

tissues, the pooled effect estimate revealed that there was a significant difference between tissue IL-35 levels in progressive, moderate, and severe subgroups ($P < 0.001$), regarding the course (Figure 3B).

A)



B)

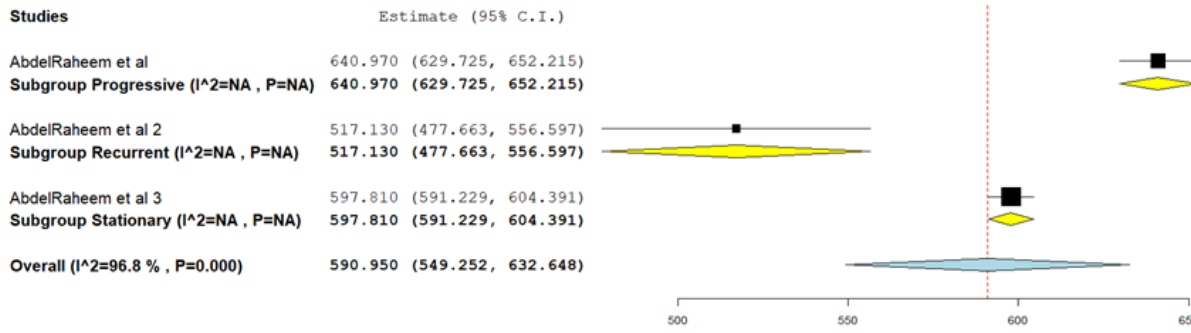
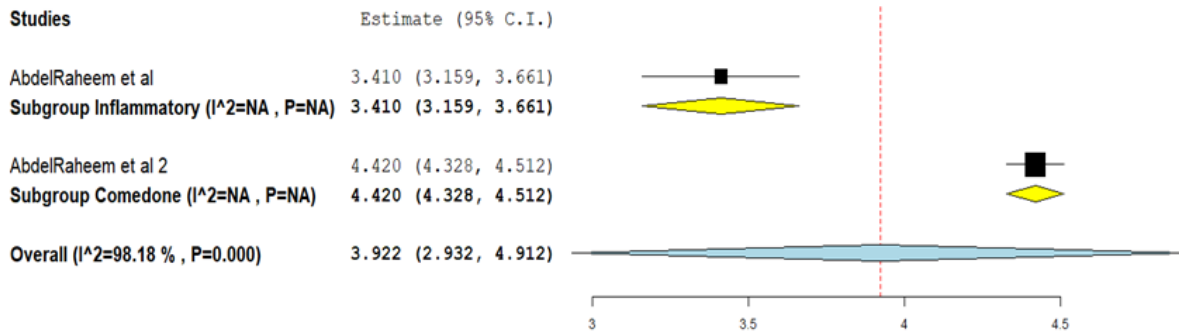


Figure 3: The pooled effect estimates of the IL-35 course of the disease in A) serum and B) tissues.

Regarding the type of lesion, the pooled effect estimate revealed that there was a significant difference between the

levels of IL-35 in serum or tissues in inflammatory and comedone subgroups ($P < 0.001$), (Figure 4).

A)



B)

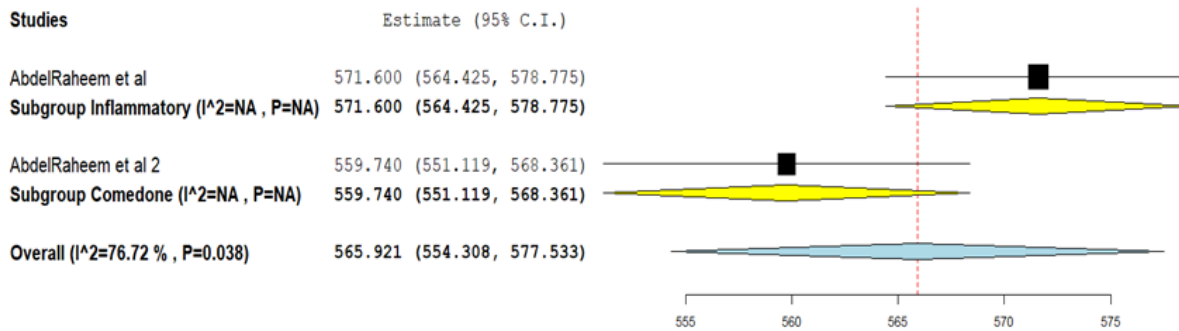


Figure 3: The pooled effect estimates of the IL-35 type of lesion in A) serum and B) tissues.

4. Discussion

Recent studies have suggested that IL-35 may be able to reduce inflammation associated with AV. In one study, researchers found that topical application of IL-35 significantly reduced inflammation in the AV. The researchers also found that IL-35 was able to reduce levels of pro-inflammatory cytokines such as TNF- α and IL-1 β , suggesting that it may be able to reduce inflammation associated with AV [8].

In addition to its potential anti-inflammatory effects, IL-35 has also been studied for its potential role in regulating

sebum production. In one study, researchers found that topical application of IL-35 was able to reduce sebum production in mice with AV. This suggests that IL-35 may be able to reduce the severity of acne by reducing sebum production and preventing clogged pores from forming. This study included two groups: The patient group included 22 patients with AV, and the second group included 22 healthy patients. The diagnosis was made on a clinical basis. Patients were of both sexes, and their ages ranged between 18 and 35 [9, 10].

By measuring the level of IL-35 in serum, the mean was 4.19 in the patient group and 1.61 in the control group. The mean of IL-35 in tissue was 551.96 in the patient group, while in the control group it was 134.82. These results revealed a highly statistically significant difference between patients and controls regarding IL-35 levels in serum and tissue.

In our study, we expected this elevation to be in relation to the grade of acne, the type of lesion, and the course of the disease, but it was not. There was no statistically significant difference between the grade and course of the disease and the type of lesion regarding IL-35 levels in serum and tissue. Exactly, we cannot explain this, but it may be due to low expression of the IL-35 receptor on CD4+ T cells that may not be sufficient enough to suppress pro-inflammatory cytokines in acne patients, like that proved in systemic lupus erythematosus, where an increased level of plasma IL-35 together with low expression of the IL-35 receptor on CD4+ T cells may not be sufficient enough to suppress pro-inflammatory cytokines in SLE patients [11].

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References

1. Lis-Święty A, Brzezińska-Wcisło L, Arasiewicz H, Bergler-Czop B. Antiphospholipid antibodies in localized scleroderma: the potential role of screening tests for the detection of antiphospholipid syndrome. *Postepy*

We have the hope to bypass any obstacle of fighting effect if there is IL-35 on this chronic miserable disease that affects young adults in the age group that needs confidence, and actually acne destroys this. If there is no relation, we need more research to explain why there is this significant high elevation of both serum and tissue levels of IL-35 in acne patients as compared to healthy controls, in contrast to the study that proved the therapeutic rule of IL-35 in systemic induced lupus in mice [11].

The use of IL-35 as a treatment for AV is still in its early stages, and more research is needed before it can be recommended as a treatment option for this condition. However, these initial studies suggest that it may be a promising new therapy for reducing inflammation and regulating sebum production associated with this condition.

Conclusion

Interleukin-35 (IL-35) is actively expressed in the serum and lesioned tissues of patients with AV. Tissue and serum IL-35 are hypothesized to play a key role in acne cure at multiple points, through their anti-inflammatory actions, but it may be hindered by unknown obstacles.

Conflicts of Interest: All authors declare no conflict of interest.

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2. Leung AK, Barankin B, Lam JM, Leong KF, Hon KL. Dermatology: how to manage acne vulgaris. *Drugs Context.* *Dermatol Alergol.* 2014;31(2):65-70. doi: 10.5114/pdia.2014.40978.

- 2021;10:2021-8-6. doi: 10.7573/dic.2021-8-6.
3. Rivera R, Guerra A. Manejo del acné en mujeres mayores de 25 años [Management of acne in women over 25 years of age]. *Actas Dermosifiliogr.* 2009;100(1):33-37. Spanish.
 4. Plewig G. Wie entsteht Acne vulgaris? [How acne vulgaris develops]. *Hautarzt.* 2010;61(2):99-100, 102-4, 106. German. doi: 10.1007/s00105-009-1829-7.
 5. Allan SE, Song-Zhao GX, Abraham T, McMurchy AN, Levings MK. Inducible reprogramming of human T cells into Treg cells by a conditionally active form of FOXP3. *Eur J Immunol.* 2008;38(12):3282-3289. doi: 10.1002/eji.200838373.
 6. Yang J, Yang M, Htut TM, Ouyang X, Hanidu A, Li X, Sellati R, Jiang H, Zhang S, Li H, Zhao J, Ting AT, Mayer L, Unkeless JC, Labadia ME, Hodge M, Li J, Xiong H. Epstein-Barr virus-induced gene 3 negatively regulates IL-17, IL-22 and ROR γ t. *Eur J Immunol.* 2008;38(5):1204-1214. doi: 10.1002/eji.200838145.
 7. Berger MJ, McKenzie CA, Chess DG, Goela A, Doherty TJ. Quadriceps neuromuscular function and self-reported functional ability in knee osteoarthritis. *J Appl Physiol* (1985). 2012;113(2):255-262. doi: 10.1152/jappphysiol.00947.2011.
 8. Rathi SK. Acne vulgaris treatment: the current scenario. *Indian J Dermatol.* 2011;56(1):7-13. doi: 10.4103/0019-5154.77543.
 9. Abd El-Raheem TA, Mohamed MH, Shaker OG, Mohamed HA. Interleukin-35 Level in Acne Vulgaris. *The Egyptian Journal of Hospital Medicine.* 2021;83(1):1509–1513. Doi: 10.21608/EJHM.2021.170520.
 10. Dos Santos ZMQ, Dos Santos MQ, Zancanaro V, Bellaver EH, Nardi GM, Gelinski JML, Locatelli C. Topical application of phenolic compounds suppresses *Propionibacterium acnes*-induced inflammatory responses in mice with ear edema. *Naunyn Schmiedebergs Arch Pharmacol.* 2019;392(5):529-540. doi: 10.1007/s00210-018-01604-z.
 11. Cai Z, Wong CK, Dong J, Chu M, Jiao D, Kam NW, Lam CW, Tam LS. Remission of systemic lupus erythematosus disease activity with regulatory cytokine interleukin (IL)-35 in Murphy Roths Large (MRL)/lpr mice. *Clin Exp Immunol.* 2015;181(2):253-266. doi: 10.1111/cei.12639.