Association of Insulin Like Growth Factor-1 and Sex Hormones in Patients of Acne Vulgaris

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Abstract

Objective: To study the relationship between serum levels of IGF-1, DHEAS, testosterone, and estradiol and the development of acne vulgaris in adolescents and young adults.

Material and Methods: This case-control study involved 140 participants (70 cases, 70 controls) from King Edward Medical University, analyzing patients with acne vulgaris aged 13-35. Serum levels of IGF-1, DHEAS, testosterone, and estradiol were estimated using ELISA techniques. The research utilized kits from renowned manufacturers and analyzed data with IBM SPSS software, setting significance at p-value ≤ 0.05.

Results: In the study of 140 participants, male and females were analyzed separately. Among 42 males (19 acne patients, 23 controls), and 98 females (51 acne patients, 47 controls) a significant association of acne vulgaris was found between elevated serum IGF-1, DHEAS, testosterone, and low estradiol levels for all male patients and for female patients < 20years of age. As for females > 20 years of age, acne vulgaris is linked to other markers but no association with testosterone levels were found.

Conclusion: The study concluded that acne vulgaris is linked to high IGF-1, DHEAS and low estradiol levels in both males and females of all age groups. While high testosterone levels are associated with acne vulgaris in all males and in < 20years of age females. Diet and genetics may also influence acne development.

Keywords: Acne development, Adolescents, DHEAS, Estradiol, IGF-1, Testosterone.

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Introduction

The human skin, spanning an average of 19 square feet, acts as a vital barrier protecting against microbial infections and chemical exposures. This complex organ, consisting of layers such as the epidermis and dermis, plays a crucial role in both innate and adaptive immunity.[1] The epidermis houses cells like keratinocytes, melanocytes, and immune cells, including Langerhans cells. The innate immune defenses utilize physical barriers, soluble factors, and pattern recognition receptors like Toll-like receptors (TLRs) to identify and fend off pathogens. Additionally, the skin harbors a diverse microbiome, with commensal microorganisms that generally coexist harmlessly. However, certain bacteria, such as P. acnes, can exacerbate skin conditions like acne vulgaris when the skin's integrity is compromised.[2]

Acne vulgaris is a prevalent inflammatory skin disorder impacting the sebaceous glands and hair follicles. It ranges from mild forms with blackheads and whiteheads to severe inflammatory types leading to scarring. The condition stems from the pilosebaceous unit, where an imbalance in keratinocyte turnover occurs[(3)]. Factors like genetics, hormones, diet, obesity, and sun exposure influence its severity and development. Studies indicate a genetic predisposition for acne, and dietary links, such as skim milk, have been suggested to exacerbate the condition.[4]

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Androgens, synthesized by adrenal glands and gonads, play a critical role in skin functions like hair growth and sebaceous gland activity, contributing to acne through hyperkeratinization of the follicular canal. Although the precise mechanisms are unclear, the interaction of androgens with growth factors and other elements promotes the formation of comedones.[5]

IGF-1, a growth factor structurally similar to pro-insulin, is pivotal in both healthy and pathological tissue development. Triggered by growth hormone, IGF-1 influences acne through its effects on cellular activities like 5-reductase activity and sebocyte proliferation. High blood glucose levels, leading to increased insulin, enhance IGF-1's role in cell proliferation, exacerbating conditions such as polycystic ovarian syndrome with associated acne symptoms. Oral hypoglycemic agents have been shown to improve insulin sensitivity and mitigate acne.[6] Acne's pathogenesis involves multiple factors: follicular hyperproliferation, excess sebum production, inflammation, and the proliferation of Propionibacterium acnes. Despite being referred to as "noninflammatory," all acne forms exhibit some inflammation level, which, interestingly, appears to precede the hyperproliferative phase.[7] Immunohistochemical studies support this, showing elevated inflammatory markers in acne patients compared to those with clear skin. The comprehensive understanding of acne's multifaceted origins is essential for developing targeted treatments that address the specific factors contributing to its development and persistence.[8] Insulin-like growth factor-1 (IGF-1) plays a crucial role in acne development, as evidenced by the lack of acne in individuals with IGF-1 deficiency, such as those with Laron syndrome. IGF-1 impacts sebum production through hormone synthesis modulation and transcription factor regulation, while dietary elements like high-glycemic carbohydrates and dairy products can alter sebum composition, facilitating P. acnes growth. P. acnes, a common skin resident, can act as an acne trigger, with certain strains promoting inflammation.[8]

Androgens play a role in sebum production and keratinocyte cell division. The precise method by which androgens contribute to acne formation is yet unknown. It has been discovered, however, that an increase in androgen levels is associated with hyper keratinization of the follicular canal and infundibulum. Androgens, growth factors, cytokines, and neuropeptides interact to trigger the production of comedones.[8]

Dietary interventions, including the Paleolithic diet, may reduce acne by influencing cellular pathways and reducing inflammation. Targeting sebum production via Acetyl Coenzyme A carboxylase could also offer therapeutic benefits.[8] Acne vulgaris is a widespread condition affecting individuals globally, ranking eighth among the most common diseases worldwide in 2010. It affects diverse ethnic groups and all ages, with approximately 85% of teenagers aged 12 to 24 experiencing acne, which can persist into adulthood. The condition varies in presentation, with adult acne often being more chronic and significantly affecting quality of life and self-perception. Gender and hormonal fluctuations heavily influence acne prevalence, with nearly 30% to 50% of teenage girls reporting psychological distress due to the condition.[9,10] Acne's chronic inflammatory nature is closely tied to sebaceous gland activity and psychological stress. Elevated IGF-1 levels during adolescence correlate with increased acne severity. A case-control study demonstrated higher IGF-1 levels in acne patients compared to controls, and treatments like isotretinoin have been shown to decrease both acne severity and IGF-1 levels.[1,11,12] The study also explores the impact of hormonal variations on acne, with androgens enhancing sebum production and estrogen and progesterone potentially reducing it. Despite normal androgen levels in most women with acne, some exhibit hyperandrogenism, linking to conditions like PCOS. This research aims to further understand the hormonal underpinnings of acne, seeking targeted treatments based on the interactions between serum levels of IGF-1, testosterone, DHEAS, and estrogen with acne vulgaris.[13]

Material and Methods

The research was a case-control study conducted in the Department of Biochemistry at King Edward Medical University, Lahore, spanning one year after ethical approval No.17042/REQ/KEMU/2019 Dated:08-10-2019. Sample collection was from patients with acne vulgaris visiting Mayo Hospital's Dermatology Outpatient Department, with analysis at the Advanced Research Centre, KEMU, Lahore. The sample comprised 140 participants (70 cases and 70 controls), determined using a specialized formula considering a 5% significance level and a 95% power of test with specific mean values for both groups. Selection favored patients aged 13-35 with acne vulgaris, no prior treatment history, excluding pregnant/lactating females, those on certain therapies, or with specific conditions like polycystic ovarian disease. Serum IGF-1 levels were estimated using the Human serum IGF-1 ELISA kit from THERMO FISHER SCIENTIFIC INC., adhering to the sandwich ELISA

principle. This assay exhibited a sensitivity of 6pg/mL, no cross-reactivity, reproducibility within 12%, and 94% average recovery from plasma samples.[14,15]

The DHEAS levels were determined using a competitive ELISA kit from ELABSCIENSE SCIENTIFIC INC (catalog number EIADHEA). DHEAS concentration was determined by plotting absorbances against a standard curve, accounting for prior dilutions.[16,17]

Testosterone levels were gauged using a Human serum testosterone ELISA kit from PerkinElmer Sciences, Inc., (UK). This is a competitive ELISA method. For serum estradiol estimation, a solid-phase ELISA technique with the kit from PerkinElmer, (UK) was employed. Absorbances were compared against standard curves to deduce hormone concentrations in samples. Data was statistically analyzed using IBM SPSS software, comparing serum levels between acne vulgaris cases and controls. Significance was established at a p-value ≤ 0.05(4, 18).

Results

In this study encompassing 140 participants, 70 acne patients were evaluated against 70 healthy, age and gender-matched controls from the same population. The average age of the acne patients (cases) was 20.6 ± 3.2 years, while the controls averaged 21.3 ± 3.4 years. Statistical analysis confirmed that the age difference between the groups was insignificant, ensuring age-matching in the study. The gender distribution was also analyzed and it was observed that among the cases, 19 were male and 51 were female. In the controls, 23 were male and 47 were female. Chi square testing indicated no significant gender difference between cases and controls. Diving into the specifics of the acne patients, the severity of acne vulgaris varied. 20 patients had mild acne, 46 exhibited moderate symptoms, and 4 had severe acne. When we correlated severity with age groups, no significant association was found. The same observation held when gender was compared to acne severity.

A primary focus of the research was to ascertain the levels of certain hormones and their potential links with acne vulgaris. Mean hormone levels were calculated and compared using independent sample t-test. p-value, odds ratio and confidence interval were also calculated to identify link of these hormone levels with development of acne vulgaris.

The serum IGF-1 levels were measured for all participants. Cases had a mean IGF-1 level of 280.65 ng/mL with a standard deviation of 35.99 ng/mL. This contrasted with the control group's mean of 155.88 ng/mL and a standard deviation of 26.85 ng/mL. Statistical evaluations revealed a significant difference between these levels, indicating a potential association of higher serum IGF-1 levels with acne vulgaris. Specifically, an odds ratio of 1.1 implied that an increase in serum IGF-1 levels heightened the likelihood of developing acne vulgaris by approximately 11%. When analyzed separately in male and female participants, the results of IGF-1 were consistent with a p-value of <0.05 and an odds ratio of >1 **(Table 2)**, indicating a positive association of high levels of IGF-1 with acne vulgaris.

For androgens and sex hormones, males and females were analyzed separately and results are displayed in Table 2. A significant association of acne vulgaris was found between elevated serum DHEAS levels, elevated serum testosterone levels, and low estradiol levels for all male patients with a p value of <0.05 and an odds ratio of >1 **(Table 2)**, indicating a positive association with acne vulgaris.

As for female participants, a significant association of acne vulgaris was found between elevated serum DHEAS levels, and low estradiol levels with a p value of <0.05 and an odds ratio of >1 (Table 2), indicating a positive association with acne vulgaris. However, for serum testosterone levels female cases have a mean value of 1.04 pg/ml and controls have a mean value of 0.54pg/ml, with a p-value of 0.09 indicating no link of serum testosterone levels with acne vulgaris in females. Patients were divided into different age groups i.e. >20 years, 20-25 years, 25-30 years and 30-35 years. When hormone levels in cases and controls were compared in different age groups, using chi-square test, the results were consistent with above mentioned findings. That is positive association of acne vulgaris was found with high serum IGF-1 levels, high serum DHEAS levels and low serum estradiol levels in both males and females of all age groups. However, for female participants, a significant association of acne vulgaris was found with elevated serum testosterone levels for patients < 20years of age with a p value of 0.018 and an odds ratio of 3.05 (Table 2). As for females > 20 years of age, acne vulgaris is linked to other markers but no association with testosterone levels were found.**(Table 2)**

In conclusion, of the various hormones examined in this comprehensive study, acne vulgaris is linked to high IGF-1, DHEAS and low estradiol levels in both males and females. While high testosterone levels are associa-

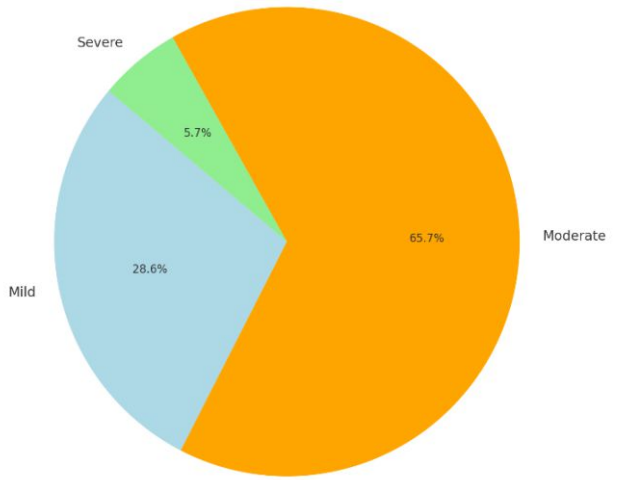
ted with acne vulgaris in all males and in < 20years of age females but not in females after 20 years of age. The research underscores the need for further investigations into the role of hormones in acne development.

The odds ratio of greater than 1 indicates that each unit increase in serum hormone levels elevates the risk of acne by more than 10%, highlighting its significant role in acne pathogenesis.

Table 1: *Frequency of severity of acne between cases*

		Cases	
		Frequency	**Percentage %**
Severity Of Acne	Mild	20	28.6
	Moderate	46	65.7
	Severe	4	5.7
Total		70	100

Fig-1: Severity distribution of acne in cases.



Discussion

In a case-control study examining the role of various hormones in the development of acne vulgaris, the serum levels of IGF-1, DHEAS, testosterone, and estradiol were compared between patients with acne (cases) and those without (controls). A total of 140 participants, aged 13 to 35, were included: 70 with acne and 70 controls. The mean ages for cases and controls were 20.6±3.28

Table 2: *Comparative Analysis of Serum Levels of IGF-1, DHEAS, Testosterone, and Estradiol in Acne Vulgaris Cases and Controls*

Hormone	Group	Mean	Std. Deviation	p-value	Odds Ratio	Confidence Interval
MALES (19 cases, 23 controls)						
IGF-1 (ng/mL)	Cases	285.94	33.45	0.00*	1.85**	1.05-1.13
	Controls	164.20	23.59			
DHEAS (ng/mL)	Cases	8.49	2.29	0.004*	1.069**	2.3-4.13
	Controls	6.72	0.67			
Testosterone (ng/mL)	Cases	11.03	2.97	0.00*	2.05**	1.5-1.9
	Controls	7.32	0.59			
Estradiol (pg/mL)	Cases	29.07	20.73	0.039*	1.52**	1.97-2.8
	Controls	39.76	4.45			
FEMALES (51 cases, 47 controls)						
IGF-1 (ng/mL)	Cases	278.69	37.03	0.00*	5.5**	6.05-7.0
	Controls	142.63	26.80			
DHEAS (ng/mL)	Cases	3.44	1.30	0.00*	4.03**	3.7-4.3
	Controls	1.95	0.50			
Testosterone (ng/mL) ≤20 years	Cases	0.951	0.664	0.018*	3.05**	4.5-5.8
	Controls	0.492	0.125			
Testosterone (ng/mL) >20 years	Cases	1.263	2.414	0.30	--	--
	Controls	0.58	0.05			
Estradiol (pg/mL)	Cases	43.37	38.78	0.04*	1.02**	1.03-1.13
	Controls	54.89	7.41			

**p-value <0.05 was significant*
*** An odds ratio greater than 1 signifies an increased likelihood of developing acne vulgaris.*

Fig-2: Comparative hormone level in males.

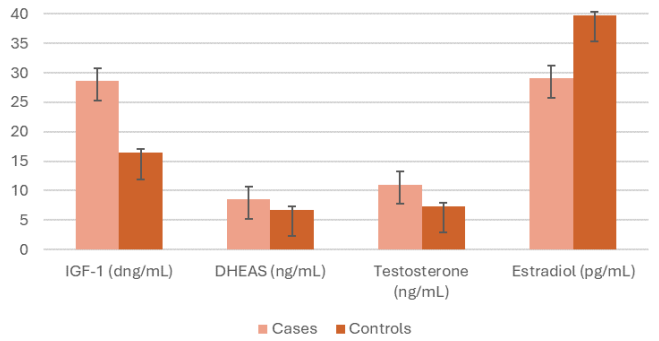
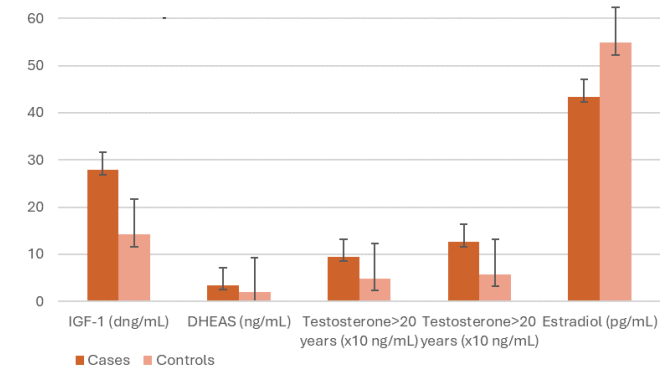


Fig-3: Comparative hormone level in females.



years and 21.34±3.45 years, respectively. Acne vulgaris is notably the tenth leading cause of DALYs in adolescence, with the highest incidence rates observed in Taiwan, Western Europe, and South Asia for the age group.[21]

The gender distribution showed a greater prevalence of acne among females, with 51 females and 19 males in the cases group. Historically, acne has manifested more prominently in females, with several studies highlighting the prevalence of premenstrual acne flare-ups. For instance, Robinson et al., 2019 reported that 60-70% of women experienced worsening acne before menstruation. The exact hormonal cause of this premenstrual flare remains ambiguous, although theories suggest changes in surface lipid composition and the impact of prostaglandins.[12] Regarding the severity, most patients exhibited moderate acne, with severe cases accounting for only 6%. The prevalence was notably higher for the age bracket 15-20, especially among females. Past research has presented varied prevalence data, possibly due to biases inherent in specific dermatology practice settings. For example, one study found an acne prevalence of 81.5% among Chinese undergraduate students, while another observed a 51% prevalence among students aged 17-25.[1]

The serum levels of IGF-1 were significantly higher in the cases (280.65±35.99 ng/mL) compared to controls (155.88±26.8 ng/mL). Previous molecular studies have associated IGF1 with increased sebum production and augmented sex hormone levels. Consequently, dietary adjustments aiming to reduce sex hormones and IGF-1 levels are sometimes suggested for acne management. Moreover, the use of drugs such as metformin, which lowers insulin-like growth factor-1, may prove beneficial, although more research is warranted.[22-23]

The role of androgens, particularly DHEAS and testosterone, in acne's pathophysiology has been documented both clinically and empirically. High levels of testosterone and DHEA-S can account for acne in both man and women. Our findings showed significant correlation between acne development and DHEAS changes. Notably, testosterone levels showed significant correlation with acne development during adolescence (i.e. <20 years of age) in females but not in adult, young females (i.e 20-35 years of age). This needs to be researched further in future studies.

Estradiol's influence on acne remains enigmatic. Generally, while androgens exacerbate acne through increased sebum production, moderate estrogen levels can suppress acne by inhibiting sebum production. Results of our study supports this argument, as low estradiol levels were linked with acne in both males and females. However, the relationship is intricate, with some women experiencing worsened acne even during high-estrogen phases like pregnancy, implying possible individual variations or other influencing factors.[24]

The study concludes that elevated serum IGF-1 levels and elevated serum DHEAS levels are significantly associated with the development of acne vulgaris, highlighting IGF-1's and DHEAS critical role in acne pathogenesis. Elevated testosterone levels also showed significant correlation with acne development in males of all ages and in adolescence females (i.e. <20 years of age) but not in adult, young females (i.e 20-35 years of age). While Estradiol levels were observed to be lower in acne patients with a statistically significant impact on acne development. These findings suggest that targeted interventions, such as dietary modifications to reduce IGF-1, DHEAS and testosterone levels or to increase estradiol levels or hormonal therapies of same affect, may benefit acne management. Future research should focus on refining severity assessments, exploring genetic predispositions, and investigating the impact of diet, particularly high-glycemic and dairy-rich foods, on acne progression. In accordance with standard research

protocols, the ethical dimensions of the study were thoroughly considered and addressed. Prior to the initiation of the research, the Ethical Review Board of King Edward Medical University, Lahore, granted its formal approval, ensuring the study's adherence to established ethical guidelines and principles. All participants were informed about the purpose, methods, and potential implications of the research. Informed consent was obtained from every participant, ensuring their voluntary involvement and their right to withdraw at any stage without consequence. Data confidentiality was maintained at all stages of the study, protecting the identity and personal information of the participants. This comprehensive ethical approach not only reinforced the integrity and credibility of the research but also prioritized the rights, dignity, and well-being of the participants involved.

Conclusion

The study concludes that elevated serum IGF-1 levels and elevated serum DHEAS levels are significantly associated with the development of acne vulgaris, high- lighting IGF-1's and DHEAS critical role in acne pathogenesis. Elevated testosterone levels also showed significant correlation with acne development in males of all ages and in adolescence females (i.e. <20 years of age) but not in adult, young females (i.e 20-35 years of age). While Estradiol levels were observed to be lower in acne patients with a statistically significant impact on acne development.

Conflict of Interest None

Funding Source None

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Authors Contribution

AH: Conceptualization of Project
NC: Data Collection
AN: Literature Search
SN: Statistical Analysis
IA, AJG: Drafting, Revision
NY: Writing of Manuscript