

Correlation of Insulin-Like Growth Factor with Acne Severity

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ABSTRACT

Background & Introduction: Insulin-Like Growth Factor-1 (IGF-1) belongs to the growth factor family, structurally resembling pro-insulin, enabling it to bind to insulin receptors. It plays an important role in many tissues including skin, particularly acne pathogenesis by stimulating sebum production and affecting androgen levels. Studies comparing IGF-1 levels in acne patients and controls have found statistically significant differences, proving acne as a sign of insulin resistance. However, no such study has been carried out in Pakistan. **Methodology:** After approval from the institutional ethical board and informed consent, a case-control study was carried out with 270 acne patients and 80 age and gender-matched controls. Patients belonged to either gender and aged between 15 – 35 years were divided into mild, moderate and severe categories. IGF-1 levels were noted after exclusion of any condition interfering with IGF-1 level and correlated with acne severity and with levels of testosterone, dihydrotestosterone (DHT) and dehydroepiandrosterone sulphate (DHEAS). Quantitative variables were expressed as median and percentiles. Comparisons were done by Mann-Whitney test and correlations by Spearman correlation. A p value of ≤ 0.05 was considered statistically significant. **Results:** Out of 350 cases and controls, There were 142 (41%) males and 208 (59%) females. In cases, there were 155 females and 115 males, whereas in controls, there were 54 females and 26 males. Median age of the patients was 20 years. Ninety-Seven patients had mild, 108 moderate and 65 had severe disease. Median levels of IGF-1 were 292 ng/m in cases. IGF-1 levels were significantly different between cases and controls and between mild and severe acne, but not between mild and moderate acne. IGF-1 levels were strongly correlated with the levels of androgenic hormones. **Conclusion:** Increase of IGF-1 levels in acne point to the role of insulin resistance and diet in acne. Future treatments may be targeted to treat IGF-1 levels by dietary interventions reducing glycemic load.

Keywords: Acne, Insulin-Like Growth Factor-1, androgenic hormones, acne severity

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INTRODUCTION

Acne is a disease of the pilosebaceous follicles with a prevalence of 22%, with acne lesions prevalent in 70 – 95% of patients.¹ The Global Burden of Disease Project ranks it as the eighth commonest disease in the world.² Environmental factors have been shown to play an important role in acne pathogenesis³ eg. family history, BMI and diet. Low glycemic diet has shown to be important in acne pathogenesis.⁴ However, it is a subject of much controversy. Insulin-like Growth Factor-1 (IGF-1) is a pleiotropic growth factor influencing normal and pathological growth. It belongs to the growth factor family which are structurally related to pro-insulin, enabling it to bind to insulin receptors.⁵ IGF-1 is produced by many tissues in response to stimulation by growth hormone. It has both autocrine and paracrine stimulation. Liver is the major source, while, in blood, it binds to IGFBP (Insulin-like Growth Factor Binding Protein). It has implications in tumour growth because of its role in cell division. Epidemiological studies show an association between IGF-1 and

risks of cancers such as related to colon, prostate and breast, as well as cartilage, nerves, bones, kidneys and liver.⁶

Although structurally and functionally similar to Insulin, it possesses distinct metabolic effects due to affinity to IGF-1 receptors, located on the majority of cells. In the skin, these are located on the epithelial cells, sebocytes, follicular outer sheath cells, eccrine glands and matrix of hair cells.⁷

IGF-1 is thought to regulate keratinocyte proliferation and sebum production in physiological doses⁸ through activation of MAPK/ERK and P1-3 K pathways. It inhibits Sex Hormone Binding Globulin (SHBG) secretion⁹ which is inversely correlated with IGF-1 levels. Insulin resistance syndromes including obesity and Polycystic Ovaries (PCOS) are associated with low SHBG levels. Insulin receptors in the cortex act like adrenal androgens in vitro.¹⁰ Therefore, adrenal androgen production may be influenced by nutritional signals. Association of IGF-1 levels with hormones in acne is seen in Laron Syndrome, a recessively inherited disorder

characterized by GH deficiency leading to inability to make IGF-1.¹¹ IGF-1 administration in humans leads to a progressive rise in Leutinizing Hormone (LH) and Testosterone in both genders and Follicle Stimulating Hormone (FSH) and androstenedione levels in females, which decreases after cessation of therapy.¹¹ Sebum production in sebaceous glands is regulated through IGF-1 through SEBRP.¹²

The role of IGF-1 in acne, although a matter of debate, has been validated by studies¹³ where IGF-1 levels were found to be elevated in acne patients (1.26 ± 0.52 U/ml) as compared to controls (0.96 ± 0.32 U/ml) $p < 0.001$, alongwith total acne lesions, comedones and inflammatory lesions.¹⁴ Effects of androgenic hormones on acne lesions were dependent on the effects of IGF-1.^{15,19} In a study examining the association of acne and serum glucose, dietary glycaemic load, overall glycaemic index and leptin levels revealed no difference between acne patients and controls in these parameters.¹⁶ Increased IGF-1 levels could be important in acne pathogenesis. No study of this kind has been published as yet in Pakistan.

METHODOLOGY

After review from the ethical board of King Edward Medical University, this case-control study was carried out in the Department of Dermatology, KEMU/ Mayo Hospital, Lahore from March, 2016 to March, 2017. Two hundred and seventy acne patients of either sex, 15-35 years of age, along with 80 age- and gender-matched controls were enrolled, after informed consent on pre-designed proformas. Patients having any condition interfering with serum IGF-1 were not included and in the case of females, pregnant and lactating females, with any clinical/radiological evidence of polycystic ovaries were excluded. Those on any treatment of acne during the last 2 months were excluded. Patients were divided into mild, moderate and severe according to the Global Acne Grading Scale.¹⁷

Blood was taken after a twelve hours overnight fast. Levels of IGF-1 and serum testosterone (T), dihydrotestosterone (DHT) & dehydroepiandrosterone sulphate (DHEAS) were measured by ELISA using chemical kits by Diasource Belgium and measured on Diamate 310. Normality of data was checked by Kolmogorov-Smirnov test. All data was entered into SPSS 20. Since the data was not normally distributed, all quantitative variables like age, weight, height, BMI and levels of hormones were expressed as medians and percentiles, Comparison between two groups was done by Mann-Whitney test and correlation between IGF-1 levels and levels of T, DHT and

DHEAS were measured by Spearman correlation. A p value of ≤ 0.05 was statistically significant.

RESULTS

There were 142 males and 208 females. In cases, there were 155 females and 115 males, whereas in controls, there were 54 females and 26 males. In both males and females, the median age was 20 years. Median age of cases was 20 years and median age of controls was 21 years. In males, in both cases and controls, the median age was 20 years. In females, in cases, the age was 20 years, while in controls, it was 21 years [Table 1].

Distribution of disease severity revealed 97 (36%) patients of mild disease, 108 (40%) of moderate disease and 65 (24%) belonging to severe disease. Comparison between age and BMI revealed that it was negatively correlated with age [Table 2].

Table 1: Age distribution

Valid (N)	350
Median (yrs)	20
Percentiles (25)	18
50	20
75	23

Table 2: Correlation of age and serum IGF levels (n = 350)

Spearman's rho		Age	IGF
Age	Correlation Coefficient	1.000	-0.041
	Sig (2 tailed)		0.449
IGF	Correlation Coefficient	-0.041	1.000
	Sig (2 tailed)	0.449	

Correlation is significant at the 0.01 level (2 tailed)

Median levels of IGF-1 were 292 ng/ml, Testosterone was 3.5 ng/ml, DHT was 184 pg/ml and DHEAS was 0.82 ug/dl in cases [Table 3].

Table 3: Level of IGF and androgenic hormones

Hormones	N	Median Value
IGF (ng/ml)	270	292
Testosterone (ng/ml)	270	3.50
DHT (pg/ml)	270	184
DHEAS (ug/dl)	270	0.82

Comparison of IGF-1 levels by Mann-Whitney test between cases and controls was significantly different with a highly significant p value [Table 4].

Table 4: Comparison of IGF between cases and controls ranks

Case Control		N	Mean Rank	Sum of Ranks
IGF ng/ml	Case	270	197.41	5313.00
	Control	80	89.97	6928.00
	Total	350		
			IGF (ng/ml)	
Mann-Whitney U			3.92	
Wilcoxin W			6.92	
Z			-8.310	
Asymp Sig (2-tailed)			0.000	

Values of IGF-1 across the spectrum of mild, moderate and severe acne showed a *p*-value to be highly significant between mild and severe (0.00) but not between moderate and severe acne. (mean

ranked 108.74 ng/ml for mild, 144 ng/ml for moderate and 159 ng/ml for severe acne respectively) [Table 5].

IGF-1 showed significant correlations with all androgenic hormones including Testosterone, DHT and DHEAS by Spearman Correlation [Table 6].

Table 5: Comparison of IGF(ng/ml) values by severity

Severity	N	Mean rank	Test Statistic ^{a,b}	IGF
Mild	97	108.74	Chi-Square	18.514
Moderate	108	144.00	df	2
Severe	65	159.06	Asymp. Sig.	.000
Total	270			

a. Kruskal Wallis Test b. Grouping Variable: severity

Table 6: Correlation between IGF & androgenic hormones (n = 350)

		IGF	Testosterone	DHT	DHEAS
Spearman's rho IGF	Correlation Coefficient	1.000	.257**	.242**	.189**
	Sig. (2-tailed)		.000	.000	.000
Testosterone	Correlation Coefficient	.257**	1.000	.566**	.549**
	Sig. (2-tailed)	.000		.000	.000
DHT	Correlation Coefficient	.242**	.566**	1.000	.498**
	Sig. (2-tailed)	.000	.000		.000
DHEAS	Correlation Coefficient	.189**	.549**	.498**	1.000
	Sig. (2-tailed)	.000	.000	.000	

** . Correlation is significant at the 0.01 level (2-tailed).

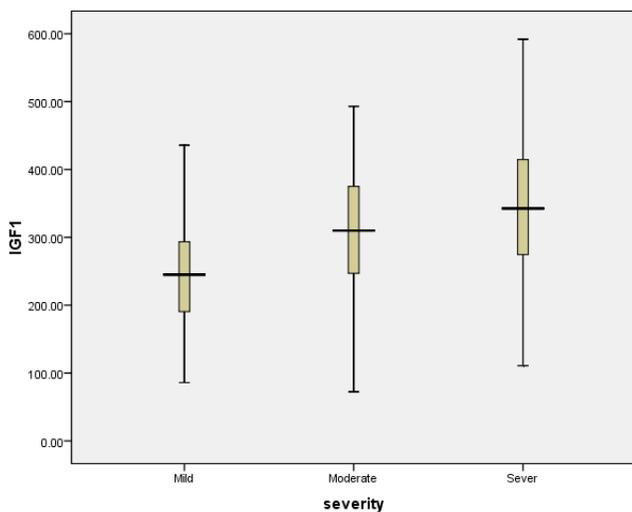


Figure 1: Relationship between IGF-1 levels and between IGF-1 levels and acne severity, where the mean ranks of mild, moderate and severe are 108, 144 & 159 ng/ml respectively, which is significant between mild and severe disease.

DISCUSSION

In the group with acne, the median age is 20 years. The age group seems to be similar to the one in India

by Rahaman *et al*¹⁵ where the mean age of cases was 19.83 years and the mean age of controls was 20.24 years. In the study carried out in Egypt,¹⁸ the mean age was 21.71 ± 4.21 in acne patients as compared to controls (21.65 ± 3.78) which is close to our study and Indonesia¹⁹ where 58% of the atients belonged to 15-20 years age group and 42% to the 21-25 years age group.

Thirty six percent patients had mild acne, compared to 40% with moderate and 27% with severe acne. In the study by Rahaman *et al*,¹⁵ 20 patients belonged to each group of mild, moderate, severe and very severe acne. IGF-1 levels were negatively correlated with age in this study, similar to other studies.²⁰ This could be related to the increase in BMI and adipose tissue with age.

In the present study, mean ranks of IGF-1 were 197 ng/ml in cases and 90 ng/ml in controls with a high level of significance (*p* value 0.00).

In the article by Aizawa H, the mean IGF-1 levels in patients with acne were 126 ± 52 ng/ml versus controls who had 96 ± 32 ng/ml. In the study by Rahaman *et al*,¹⁵ the mean IGF-1 level for cases was 148.78 ± 73.84 ng/ml while in controls it was 127.18 ± 55.71 ng/ml. In the study by Saleh *et al*,¹⁴ IGF-1 levels in controls was 243.23 ± 59.54 ng/ml, while in

mild acne, it was 335.18 ± 18.15 ng/ml, in moderate 365.18 ± 16.97 ng/ml and severe 440.76 ± 46.71 ng/ml. Hence, the results are closer to India probably due to similarities in ethnicity.

In this study, IGF-1 levels were significantly associated with acne severity (p value 0.00) by Spearman correlation. (mean ranked 108.74 ng/ml for mild, 144 ng/ml for moderate and 159 ng/ml for severe acne respectively).

In the study by Saleh *et al.*¹⁸ IGF-1 was significantly associated with the severity of acne, where the values were 335 ng/ml, 365 and 440 ng/ml in mild, moderate and severe acne while in controls it was 243 ng/ml ($p=0.001$).

In the study by Rahaman *et al.*,¹⁵ mean plasma IGF-1 level in acne was significantly higher ($p=0.49$) 148.78 ± 73.84 ng/ml than in controls (127.18 ± 55.71 ng/ml).

It was also significantly different in different grades of acne ($p=0.04$), where there was an increase in IGF-1 levels with different grades of acne severity ($p=0.04$).

In the study by Wulan *et al.*,¹⁹ serum IGF-1 levels in the mild acne were 155 ± 23.38 ng/ml and in moderate 211.052 ± 85.498 ng/ml.

Samar *et al.*²¹ also found a significant difference in IGF-1 levels between patients and controls. However, in contrast to other studies, serum IGF-1 level was found to be lower in mild acne as compared to moderate or severe acne.

In this study, IGF-1 values correlated strongly with all the androgenic hormones. The increased levels of IGF-1 correlate with an increase in the severity of acne.¹⁵

Regarding the relationship of IGF-1 with other hormones, in the study by Aizawa *et al.*,²² levels of IGF-1 in patients with acne were significantly greater than those of controls (1.26 ± 0.52 U/ml) vs (0.96 ± 0.32 U/ml) ($p<0.001$). Six (7%) had elevated IGF-1 levels, but there were no significant correlations between IGF-1 and T, DHT or DHEAS levels or between IGF-1 and acne severity.

Since the measurement of serum IGF-1 levels is a convenient indicator of GH secretion, the increase of serum IGF-1 levels seen in some acne patients might reflect an increase of GH.

In another study, acne patients had elevated IGF-1 and DHT levels as compared to controls, while there was no statistically significant difference in men.¹⁴ Emerging studies show acne as a sign of insulin resistance with a higher fasting glucose level.²³

Circulating IGF-1 levels are used as a substitute of IGF-1 reactivity. However, in vivo levels are determined by local concentration of IGF binding proteins, not mentioned here.

CONCLUSION

Implications of increased IGF-1 levels in acne suggest acne as a syndrome of insulin resistance, also predicting its severity. Studies aimed at reducing the level of IGF-1 either by medications targeting high serum levels or dietary interventions should be the future course of action in these patients.

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