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Acne Vulgaris Severity Correlation with Serum Calprotectin: A Prospective Case-Controlled Study

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ABSTRACT

Background: Acne vulgaris is an inflammatory skin disease which is extremely common. Acne affects around 85% of teenagers, and its effects can persist into adulthood for some. It has been hypothesized that calprotectin plays an inflammatory function in acne vulgaris, and so contributes to its etiopathogenesis.

Objective: The aim of the current study was to measure serum calprotectin in patients with acne vulgaris and finds any links between that measure and the severity of the underlying condition.

Patients and methods: A total of 45 people with a diagnosis of acne vulgaris and 45 controls of the same age and sex participated in the study. They were selected from the Dermatology, Andrology, and STDs outpatient clinic at Mansoura University Hospitals between May 2021 and May 2022.

Results: Acne vulgaris patients had considerably higher serum calprotectin levels with median of 18.9 compared with a median of 11 of the healthy volunteers (P <0.001). The GAGS (Global Acne Grading System) score was positively correlated with age (r= 0.341, P =0.022), body mass index (r= 0.538, P <0.001), acne duration (r= 0.461, P <0.001), and serum calprotectin (r= 0.874, P <0.001). GAGS scores was also positively correlated with serum calprotectin (r= 0.943, P <0.001), acne duration (r= 0.523, P <0.001), and age (r= 0.392, P =0.008).

Conclusion: Acne vulgaris patients had increased serum calprotectin levels compared to control subjects, and they have a statistically significant relationship with disease severity, suggesting that calprotectin may be used as a chemical biomarker to determine disease severity.

Keywords: Acne Vulgaris, Serum Calprotectin, GAGS score.

INTRODUCTION

Pilosebaceous unit inflammation is chronic and widespread in acne vulgaris (AV). The precise pathology of AV is unknown, despite the fact that different pathways have been implicated in its etiopathogenesis [(1)]. The etiopathogenesis of AV involves a number of variables. Increased sebum production, aberrant hyperkeratinization, altered microbial flora, and inflammation are the primary causes [(2)].

While the precise timing of these occurrences is yet unknown, inflammation has been hypothesized to be the first cause. Propionibacterium acne plays a crucial part in the mechanisms that initiate and sustain the inflammatory response, but these mechanisms are not yet fully understood [(3,4)].

Acne-causing Propionibacterium can cause inflammation in two ways. The production of inflammatory cytokines and antimicrobial peptides is boosted. Toll like receptor 2 activation by Propionibacterium acnes also triggers the innate immune response (TLR2) [(5)]. The pilosebaceous unit consists of the sebaceous gland, the hair follicle, the arrector pili muscle, and the sebaceous duct. Together with keratinocytes, sebocytes play a role in immunity[(6)].

S100A8 and S100A9, both members of the S100 protein family, heterodimerize to generate calprotectin, a protein involved in a wide range of inflammatory responses [(7)]. The proinflammatory response may be amplified by epithelial calprotectin secretion [(8)].

Leukocyte migration, infection as well as cytoskeleton modulation are all areas where calprotectin comes into play. In addition, calprotectin has a direct antibacterial impact by binding to zinc and manganese, two metals that are essential for bacterial growth [(1)].

Serum calprotectin level increases in various diseases as inflammatory diseases, autoimmune diseases and cancers [(9,10)].

It has been hypothesized that calprotectin plays an inflammatory function in acne vulgaris, and so contributes to its etiology. Patients with moderate-severe acne had higher serum calprotectin levels than those with mild acne, while AV patients had higher serum calprotectin levels than controls overall [(1)].

The aim of the current study was to measure serum calprotectin in patients with acne vulgaris and finds any links between that measure and the severity of the underlying condition.

PATIENTS AND METHODS

A total of 90 subjects were recruited for this case control study. They were selected from the Dermatology, Andrology, and STDs outpatient clinic at Mansoura University Hospitals between May 2021 and May 2022. Recruited participants were divided into 2 groups; Case group: 45 acne vulgaris patients, and control group: 45 healthy controls of matched age and sex.

Sample Size:

IBM SPSS SamplePower version 3.0.1 (IBM a Corp., Armonk, NY, USA) was used to determine the minimum sample size needed for the study.

Korkmaz and Fıçıcıoğlu[(1)] conducted a comprehensive literature search and determined that the mean **GAGS (Global Acne Grading System)** score in the cases of

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acne vulgaris reported in the study was 21.76 (SD 3.66). A sample size of 45 cases will have 80% power to detect a 1.5 points difference in the mean GAGS score, with a 0.05 two-sided significant level.

An equal number of healthy controls were recruited:
Inclusion criteria: Patients with acne vulgaris aged 15-30 years not receiving topical nor systemic treatment for at least three months.

Exclusion criteria:

1. Patients with systemic disease such as malignancies, inflammatory illnesses, and autoimmune diseases which is likely to be associated with increased level of calprotectin.
2. Pregnant and breastfeeding.
3. Patients using non-steroidal anti-inflammatory drugs such as diclofenac [(11)] or hormonal medicine such as glucocorticoids [(12)], as they are a known sources of increased fecal calprotectin levels**.**

All participants were subjected to the following:

1. **Complete history taking** including age, sex, occupation, marital status, special habits, dietary intake, associated psychological disturbance, associated medical or surgical conditions and drug intake.
2. **General examination.**
3. **Dermatological examination to assess the distribution of the lesion**: Assessment of disease severity using GAGS [(13)]**.**

To use it, you'll divide your face, chest, and upper back into six sections: **GAGS Location factor:** Forehead factor is 2. Right cheek factor is 2. Left cheek factor is 2. Nose factor is 1. Chin factor is 1. Chest and upper back factor are 3.

A value (Grade) is assigned to each type of lesion based on its degree of severity. Because there are no lesions, the answer is 0. comedones = 1, papules = 2, pustules = 3, nodules = 4.
Each location's score (its "Local score") is calculated by multiplying the area factor by the severity grade of the most severe lesion found there.

The severity was graded as: Mild with score 1-18. Moderate with score 19-30. Severe with score 31-38. Very sever if the score is more than 38.

Assessment of serum calprotectin by ELISA method: Everyone who participated in the study had a blood sample taken from their periphery. After letting the blood samples coagulate for 30 minutes, they were centrifuged at 1000 g for 15 minutes. Urgent analysis was performed on collected serum samples, or samples were frozen and analyzed later. All participants had their serum calprotectin levels tested with human calprotectin (ELISA) kits. Bioassay technology, lab Mahdist, Jiaxing, Zhejiang, China, Cat. No. E 40 10 Hu, was used in accordance with the manufacturer's instructions.

Ethical consideration

Mansoura Faculty of Medicine's Institutional Review Board (IRB) approved this protocol (MS.21.03.1397). Written informed consent of all the participants was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 23.0 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Quantitative data was represented by numbers and percents. All quantitative data were first subjected to Shapiro-test Wilk's of normality, with a normal distribution being assumed if the p value was greater than 0.050. If the data were normally distributed with no outliers, they were reported as mean, SD; otherwise, the median and interquartile range (IQR) were used (Q3 minus Q1). Chi-square test was used to compare categorical data between groups if anticipated counts in all cells ≥5; otherwise, Fisher's exact test was employed. The Mann-Whitney U test was used to compare two groups' non-normally distributed data. Since all of the data fell into the "normal" category, we conducted a one-way ANOVA to see how the three groups of people fared against one another. Significant results were followed by post-hoc Tukey HSD tests to discover where was that difference occurs. The degree and direction of relationship between two continuous variables were evaluated using Spearman's correlation. If the correlation coefficient is below 0.3, between 0.3 and 0.5, or above 0.5, the strength of the link is small, medium, or large, accordingly. Partial correlation was used to determine the direction and strength of link between two continuous variables after correcting for additional variables. Acne versus control, or severe versus mild acne, were two scenarios for which a cutoff value of a continuous variable was determined using ROC curve analysis. When the probability level was equals or less than 0.05, it was judged to be statistically significant.

RESULTS

Table 1 shows that compared with the control group, the acne group had a considerably larger number of participants with a high glycemic diet and a positive family history of acne, as well as significantly higher serum calprotectin. In terms of gender, age, smoking status, height, weight, and body mass index (BMI) , the 2 groups did not differ (P>0.05).

Table (1): Comparisons of clinico-demographic and laboratory data between two groups

Parameter	Control group N=45	Acne group N=45	P value
Sex Male Female	 24 (53.3%) 21 (46.7%)	 23 (51.1%) 22 (48.9%)	 0.833
High glycemic diet	10 (22.2%)	23 (51.1%)	**0.004**
Current smoking	7 (15.6%)	7 (15.6%)	1.000
Family history of acne	10 (22.2%)	23 (51.1%)	**0.004**
Age (years)	21 (19.5 – 25.5)	21 (19 -26)	0.984
Weight (kg)	68 (58 – 71.5)	68 (59.5 – 75)	0.674
Height (meter)	1.68 (1.57 – 1.70)	1.65 (1.59 – 1.70)	0.855
BMI (kg/m^2)	24.2 (23.4 – 25.8)	24.5 (23.7 – 26.0)	0.366
Serum calprotectin (µg/ml)	11 ± 2.74	18.9 ± 4.61	**<0.001**

Notes: Data is N (%) for categorical variables (test of significance is Chi-Square test), and median (Q1-Q3) for quantitative variables (test of significance is Mann-Whitney U-test). M : F = Male : Female.

Cutoff value for serum calprotectin in discriminating acne from healthy control (Figure 1): A cutoff value more than 13 µg/ml is a prefect discriminator (AUC = 1.000, with 100% sensitivity, and specificity).

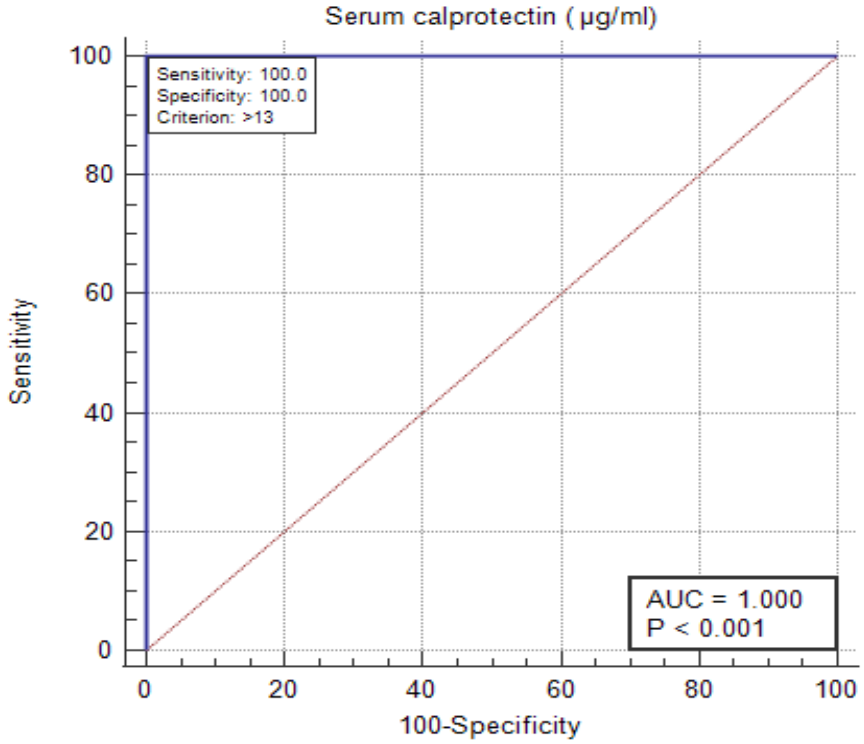

Figure (1): A ROC curve analysis was run to find a cut-point that can discriminate acne form control subjects.

Results of acne group (N=45):

This group involved 45 cases divided into three equal subgroups (N =15 per subgroup) based GAGS: **Subgroup 1:** Mild (GAGS = 1-18). N (%) = 15 (33.3%). **Subgroup 2:** Moderate (GAGS = 19-30). N (%) = 15 (33.3%). **Subgroup 3:** Severe (GAGS = 31-38). N (%) = 15 (33.3%). Table 2 shows a statistically significant difference between the three GAGS grades for age, acne duration, weight, height, BMI, and serum calprotectin.

Table (2): Comparisons of the acne group cases according to sociodemographic characteristics and serum calprotectin.

Characteristic	Mild	Moderate	Severe	Total	P value
Sex Male Female	 6 (40%) 9 (60%)	 7 (46.7%) 8 (53.3%)	 10(66.7%) 5 (33.3%)	 23 (51.1%) 22 (48.9%)	 0.315*
High glycemic diet	9 (60%)	9 (60%)	5 (33.3%)	23 (51.1%)	0.241*
Current smoking	1 (6.7%)	2 (13.3%)	4 (26.7%)	7 (15.6%)	0.463$
Family history of acne	7(47.6%)	7 (47.6%)	9 (60%)	23 (51.1%)	0.701*
Age (years)	20.5 ± 3.2	23.3 ± 4.4	24.3 ± 4.0	21 (19 -26)	**0.033**
Duration of acne (months)	16.4 ± 3.51	32.9 ± 8.1	45.6 ± 10.6	24 (12 – 48)	**0.001**
Weight (kg)	61.2 ± 6.6	67.3 ± 8.7	75.3 ± 8.3	68 (59.5 – 75)	**<0.001**
Height (meter)	1.61 ± 0.07	1.64 ± 0.07	1.68 ± 0.05	1.65 (1.59 – 1.70)	**0.016**
BMI (kg/m^2)	23.61 ± 1.05	25.08 ± 1.93	26.70 ± 2.45	24.5 (23.7 – 26.0)	**<0.001**
Serum calprotectin (µg/ml)	15.75 ± 1.28	18.72 ± 0.38	20.63 ± 1.55	18.9 ± 4.12	**<0.001**

Notes: Data is N (%) for categorical variables, test of significance is *Chi-Square test, or $Fisher's exact test. Data is mean ± standard deviation for quantitative data; test of significance is One-Way ANOVA.

Table 3 shows a statistically significant positive correlation between GAGS score and age, height, and acne duration (medium strength), and weight, BMI, and serum calprotectin (large strength). Results also demonstrate a favorable association between GAGS scores and age, height (medium strength), weight, BMI, acne severity, and serum calprotectin levels (large strength).

Table (3): Correlation between GAGS and study parameters.

Parameter	GAGS score		GAGS grades	
	r_s	P value	r_s	P value
Age (years)	0.341	**0.022**	0.392	**0.008**
Weight (kg)	0.630	**<0.001**	0.624	**<0.001**
Height (meter)	0.488	**0.001**	0.438	**0.003**
BMI (kg/m^2)	0.538	**<0.001**	0.565	**<0.001**
Serum calprotectin (µg/ml)	0.874	**<0.001**	0.943	**<0.001**
Duration of acne (months)	0.461	**0.001**	0.523	**<0.001**

Notes: r_s = Spearman's correlation coefficient.

After controlling for age, body mass index, and acne duration, the correlation between serum calprotectin and GAGS score was analyzed using Pearson's partial correlation. When controlling for age (rpartial= 0.820, P 0.001), BMI (rpartial= 0.801, P 0.001), and acne duration (rpartial= 0.793, P 0.001), the strength of this linear connection remained sizable (Pearson's partial correlation).

Post-hoc Tukey's HSD tests show the following significant pairwise comparisons: The correlation between age and severity increases dramatically beyond chance. Severe acne lasts longer than mild acne by a large margin. The difference in BMI between severe and mild or moderate instances is statistically significant, but not between moderate and mild cases. Severe cases have much greater average heights than moderate cases. Significantly higher BMI in severe cases compared to mild ones. Serum calprotectin: substantially increased in severe compared to moderate and mild.

Accuracy of serum calprotectin in discriminating the three GAGS grades: Figure 2 shows that serum calprotectin at cutoff value of >17.9 µg/ml can perfectly discriminate moderate from mild cases of acne.

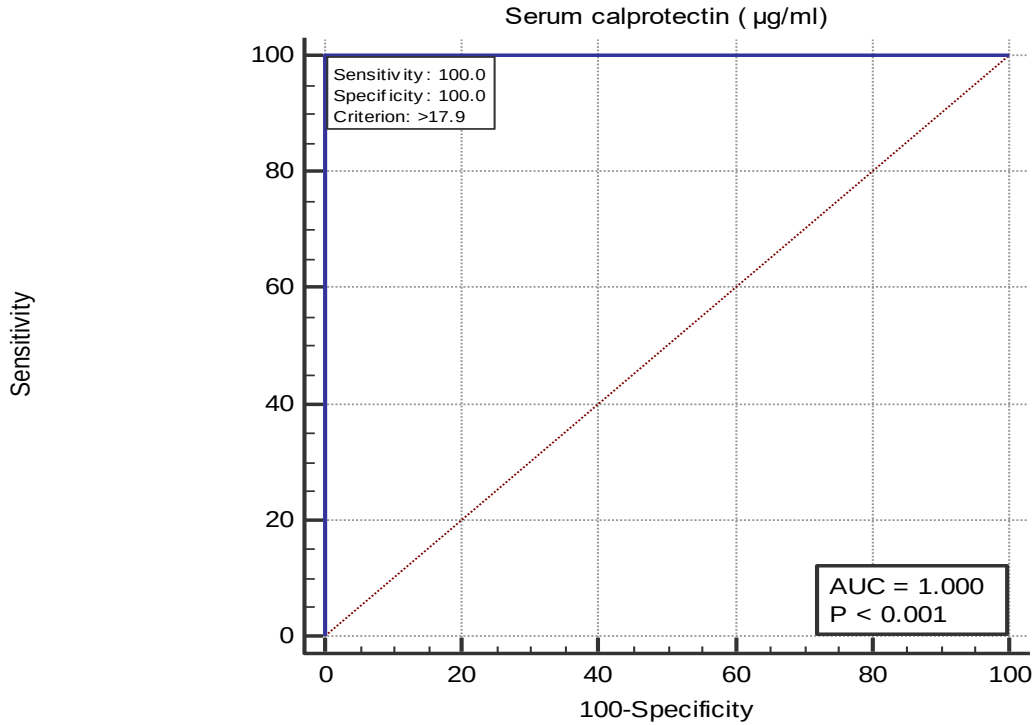

Figure (2): Discriminating moderate from mild cases.

Figure 3 shows that serum calprotectin at cutoff value of >19.2 µg/ml can perfectly discriminate severe from moderate cases of acne.

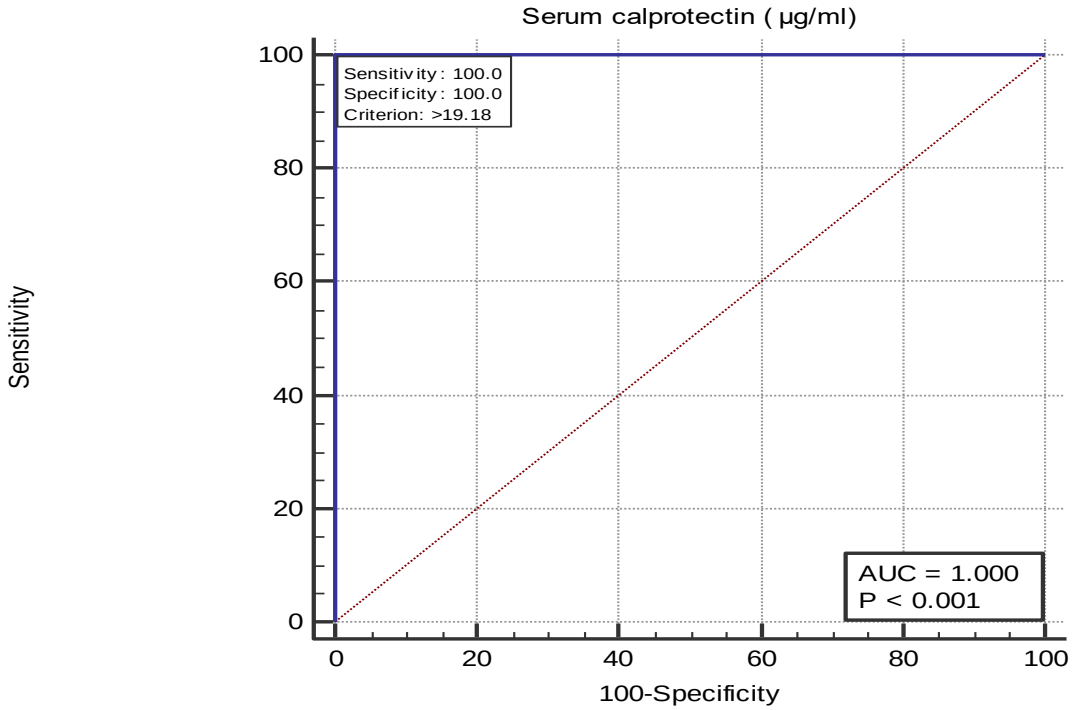

Figure (3): Discriminating severe from moderate cases.

Figure 4 shows that serum calprotectin at cutoff value of >17.9 µg/ml can perfectly discriminate moderate from mild cases of acne.

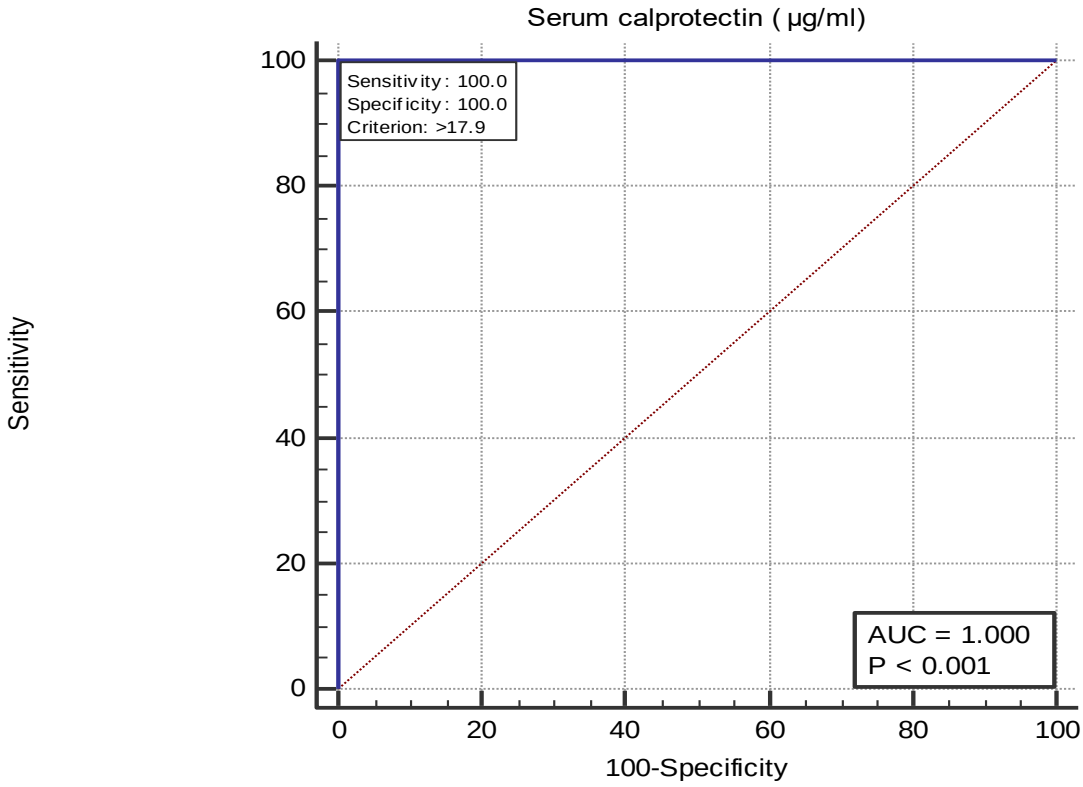

Figure (4): Discriminating severe from mild cases.

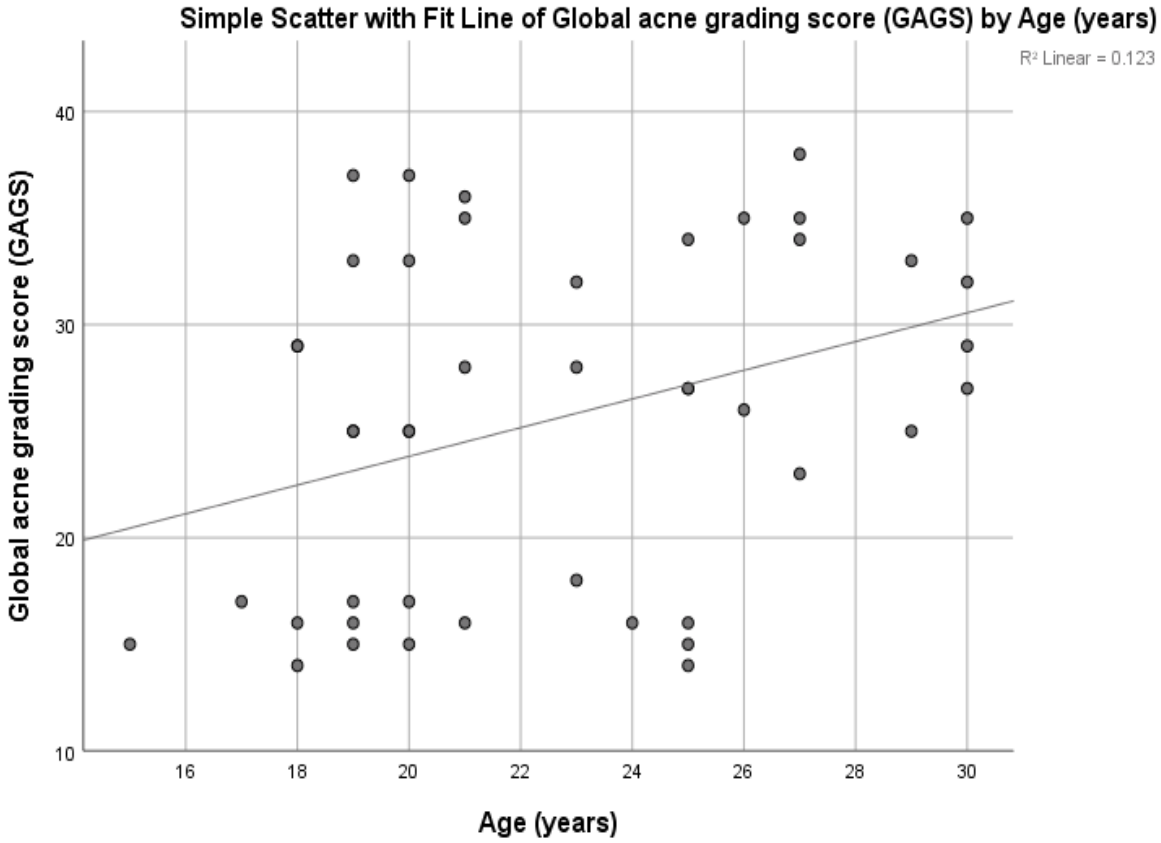

Figure (5): Scatterplot for correlation between GAGS and age.

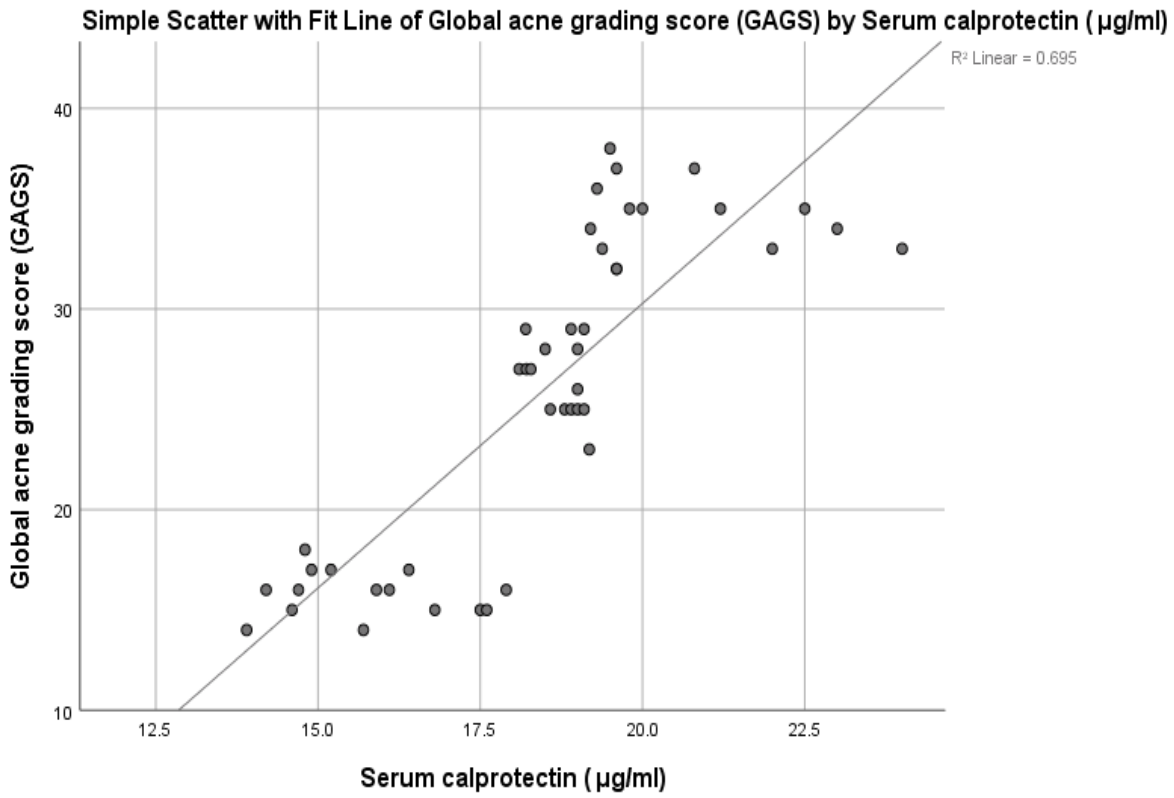

Figure (6): Scatterplot for correlation between GAGS and calprotectin.

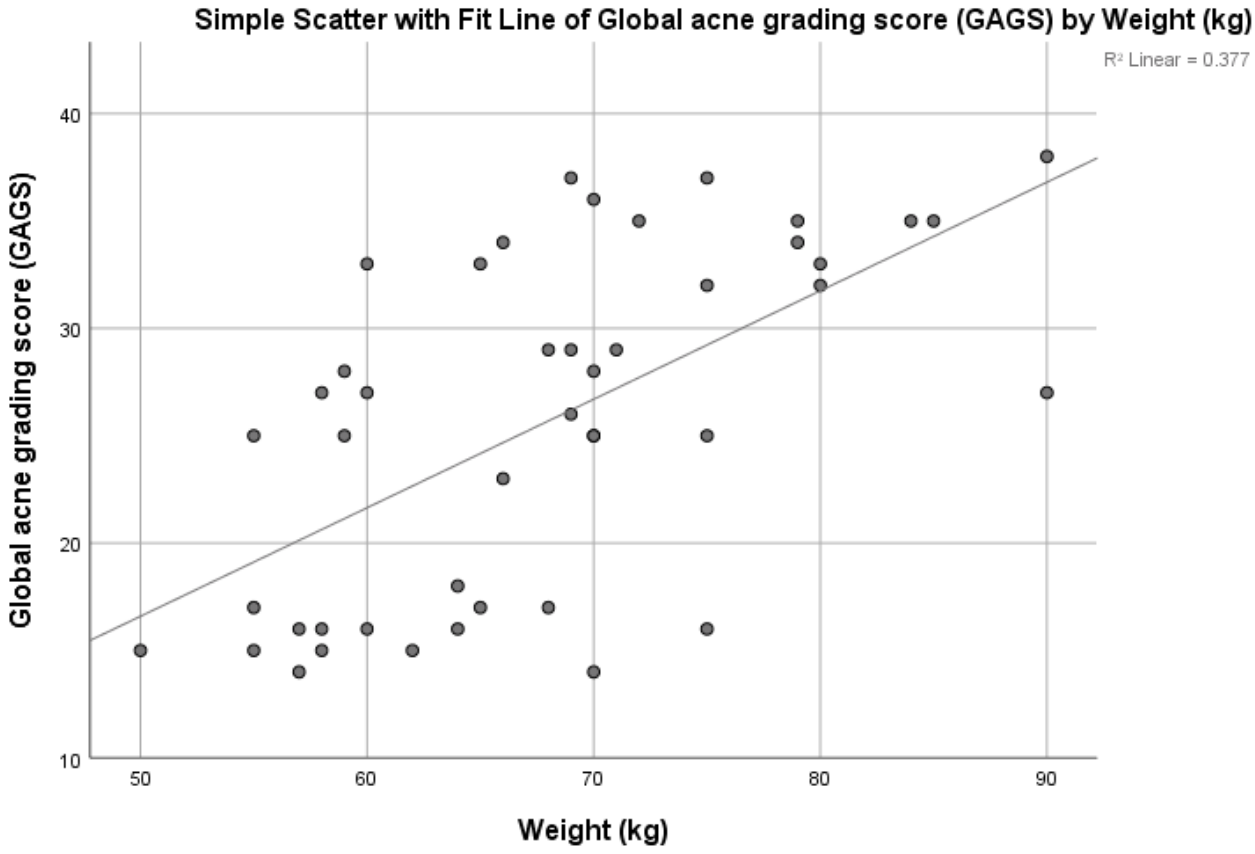

Figure (7): Scatterplot for correlation between GAGS and weight.

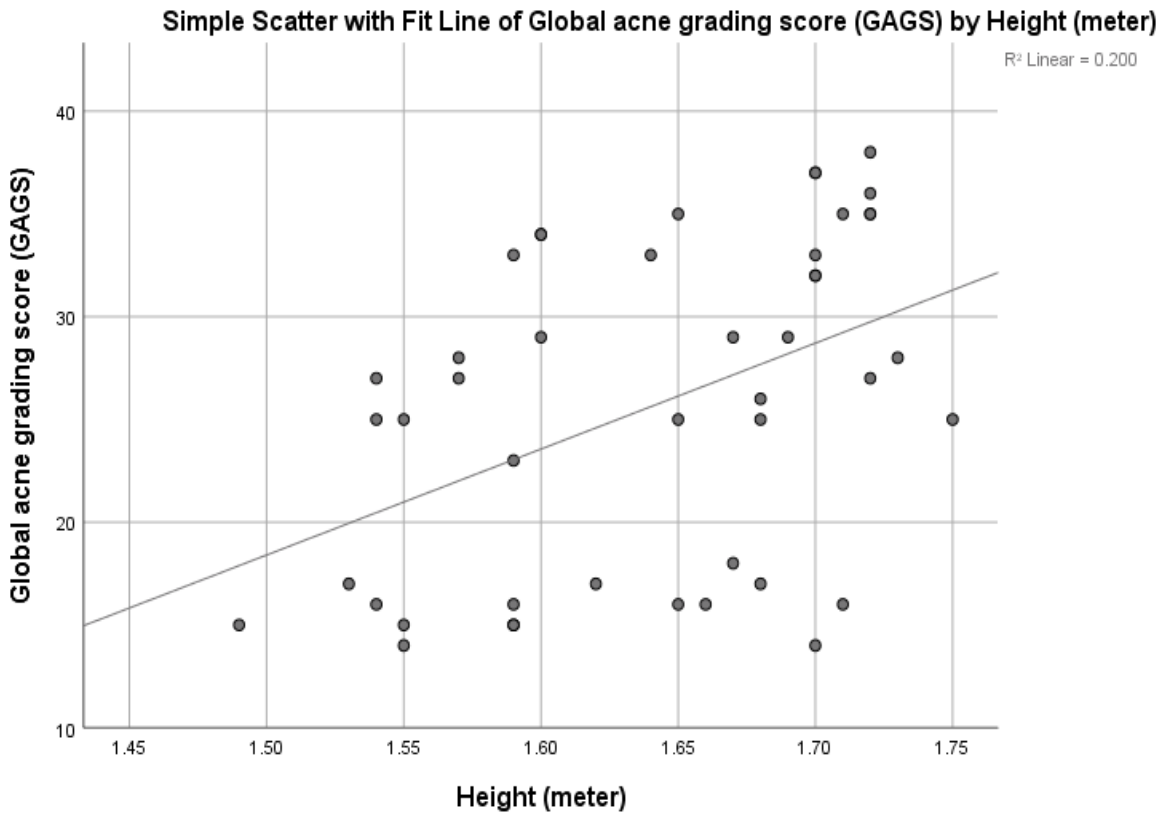

Figure (8): Scatterplot for correlation between GAGS and height.

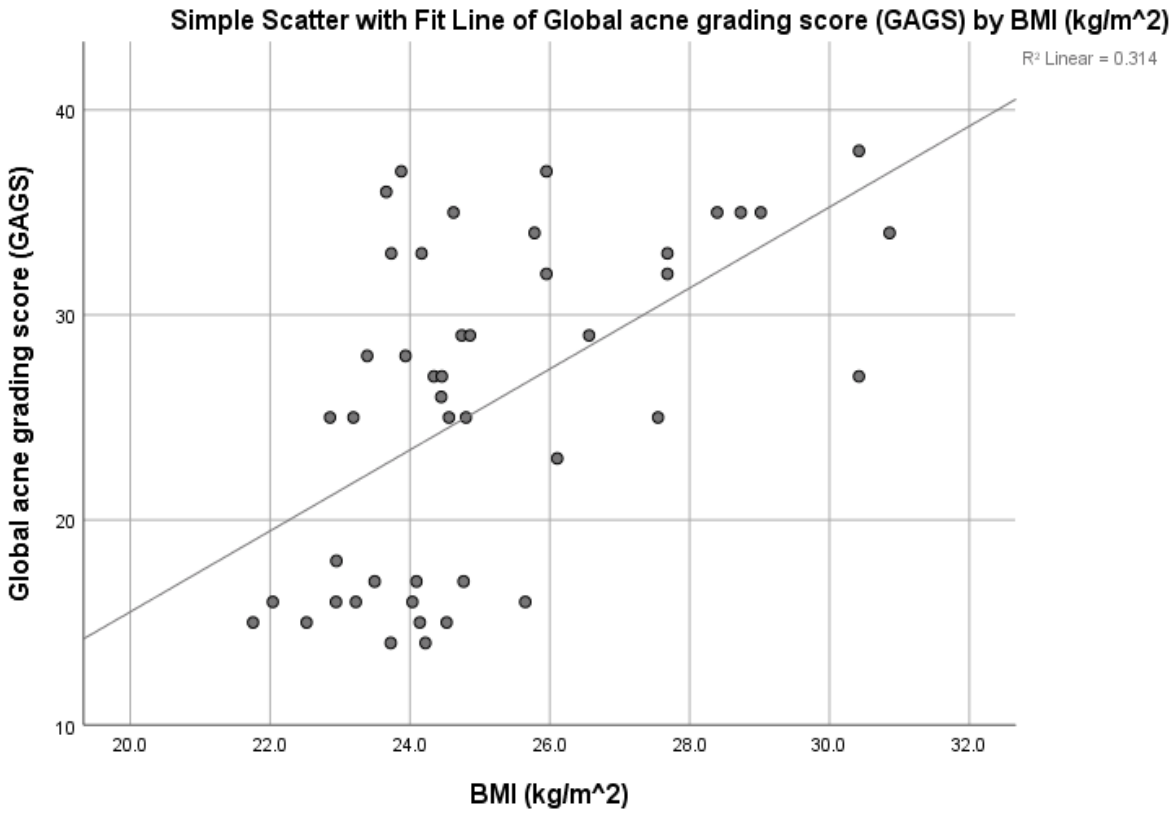

Figure (9): Scatterplot for correlation between GAGS and BMI.

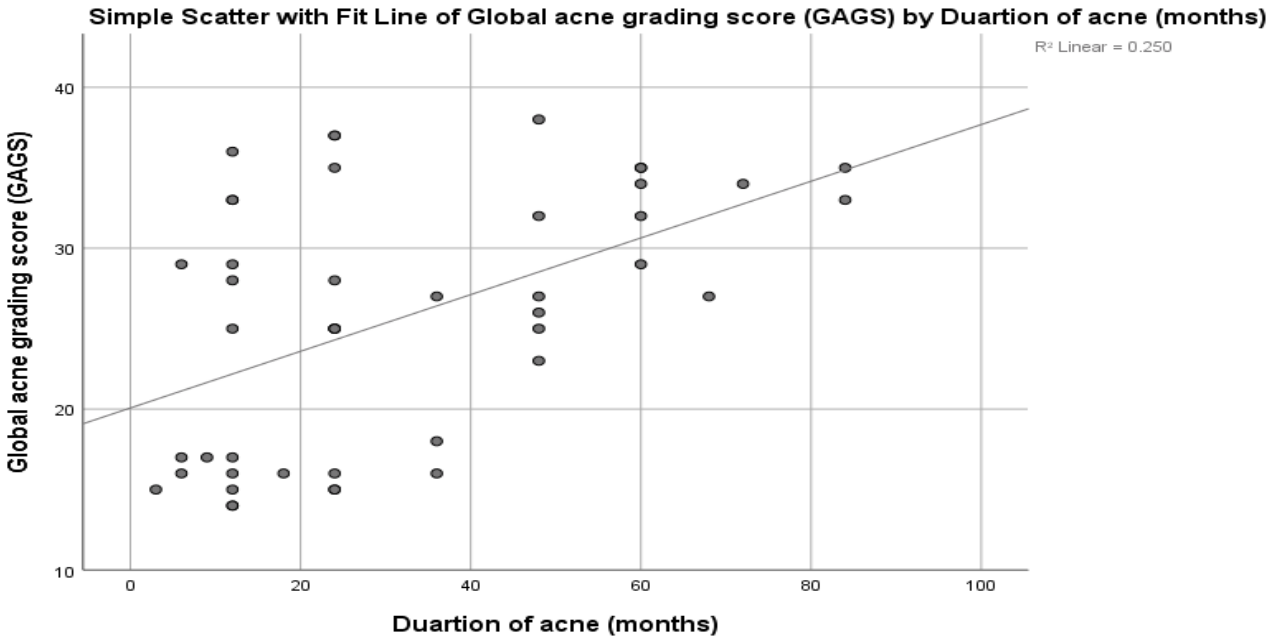

Figure (10): Scatterplot for correlation between GAGS and acne duration.

DISCUSSION

In the present study, there was no statistically significant difference between the two groups as regards sex, age, current smoking, weight, height, and BMI. **But,** there was a statistically significantly higher proportion of high glycemic diet and positive family history of acne in acne group vs. control subjects (P=0.004).

Regarding family history among acne cases, in line with our results Alsalem *et al.* [14] reported that 55% of the studied cases have positive family history of acne vulgaris. **Heng and Chew** [15] also observed an increased risk of acne in children with a parental history of the condition. **Similarly,** a total of 59.8% of participants in the study by **Kaminsky *et al.*** [16] had a positive family history of acne.

Cordain and colleagues [17] reported that acne rates in the West may be higher than they would be without the high glycemic diets that are so common there. It was speculated that the hormones and bioactive compounds found in milk and dairy products could exacerbate acne. There were fifty-two patients in **George and Sridharan's** [18] study who had a direct link between the foods they ate and the worsening of their lesions. A total of 41 (37.3%) people reported worsening symptoms after eating greasy food, 21 (20.9%) people after eating meat, and 11 (10%) people after eating a high glycemic diet. Only 2 (1.8%) patients reported worsening symptoms following consumption of dairy products, while 8 (7.3%) patients reported worsening symptoms following consumption of nuts and chocolates.

In the current study, Serum calprotectin was substantially greater in the acne group [18.9 (16.6 - 19.6)] than in the control subjects [11 (10.3 - 12.5)] (P< 0.001).

In the same line, Abd Allah *et al.* [19], Basha *et al.* [20], Fouda *et al.* [21] and **Farag *et al.*** [22] serum calprotectin levels were shown to be considerably higher in patients with acne vulgaris compared to healthy controls, indicating that calprotectin may be a valuable measure in evaluating the severity of acne vulgaris.

Fouda *et al.* [21] found that the serum calprotectin levels of the case (16.52±9.27) and control (1.73±1.90) groups were significantly different. Serum calprotectin levels in acne vulgaris patients were significantly greater than in the control group, as shown by **Farag *et al.*** [22]**,** with a difference of 3.86 (SD 2.58) pg/ml (P <0.001) and 0.29 (SD 0.14) (P <0.001). **In contrast, Nasr *et al.*** [23] blood calprotectin levels were found to be greater in individuals with acne vulgaris compared to controls, however the difference was not statistically significant.

A link between calprotectin and acne has been postulated through a number of mechanisms, however these investigations were unable to determine the exact mechanism by which calprotectin contributes to acne. First, the inflammatory infiltrate of acne lesions is made up of both early lymphoid infiltrate and late polymorphonuclear leukocytes. Higher numbers of CD3+ and CD4+ T cells, as well as macrophages, were found in the perifollicular and papillary dermis of a patient with no visible acne lesions, suggesting that inflammation may be the source rather than the effect of comedo formation and bacterial colonization [24]**.**

Second, p-acnes has been shown to increase MMP-9 keratinocyte production and release, which contributes to inflammation, both in vivo and in vitro, during the first few hours of incubation with acne lesions' epidermis. TLR4 acts as an agonist on the S100A8/S100A9 complexes. Furthermore, this may shed light on the connection between acne and calprotectin [25]**.**

The present study showed a significant positive correlation between GAGS score and age (r=0.341,

P=0.022), height, weight, BMI (r=0.538, P <0.001), acne duration (r=0.461, P=0.001) and serum calprotectin (r=0.874, P <0.001)**. It also showed** a significant positive correlation between GAGS grades and age (r=0.392, P=0.008), height, weight, BMI (r=0.565, P <0.001), acne duration (r= 0.523, P <0.001), and serum calprotectin (r=0.943, P <0.001).

In detail, our study revealed that both the average age and the average length of time that someone has had acne were considerably greater for those with severe cases than those with mild cases. The difference in body weight between severe and mild or moderate instances was statistically significant, while the difference between mild and moderate cases was not. Severe cases had much greater height than moderate cases. The severe cases had a much higher body mass index than the mild ones. There was a clear gradient from severe to moderate to mild in terms of serum calprotectin.

Mohamed *et al.* [26] results showed that differences in gender, acne subtype, or disease duration had no effect on the trend of worsening AV. However, the severity of AV was found to correlate strongly with plasma calprotectin concentration. Furthermore, there was a statistically significant inverse link between the age of patients and the severity of acne, suggesting that AV is more severe in younger individuals. There was no statistically significant relationship between plasma calprotectin levels and calprotectin levels in papules and other inflammatory lesions in the patient group. Calprotectin levels in comedones, which are non-inflammatory lesions, correlated strongly with plasma Calprotectin levels in patients.

Regarding correlation between serum calprotectin level and acne severity in case group our result came in agreement with **Basha *et al.*** [20] study results, the study results showed a significant positive correlation between serum calprotectin levels and the severity of acne. This was in line with **Fouda *et al.*** [21] who reported similar results. Similarly, the amount of serum calprotectin was found to have a strongly important positive association with GAGS score (r=0.854; P <0.001) in **Abd Allah *et al.*** [19] **study**. In a study conducted by **Korkmaz and Fçcolu** [1], it was shown that the serum calprotectin levels of people with moderate-severe AV were statistically substantially greater than those of people with mild AV (P <0.001). It was also found that mild AV patients had a greater serum calprotectin level compared to healthy controls (P =0.047). Spearman's correlation analysis, however, showed no association between serum calprotectin levels and GAGS in AV patients (r=0.1179; P =0.171).

Serum calprotectin levels were not correlated with demographic or clinical characteristics of acne vulgaris patients (including age at illness onset, disease duration, site of lesion, disease course, or GAGS score) in a research by **Farag *et al.*** [22] (P >0.05 for all).

Abd Allah *et al.* [19] findings, on the other hand, revealed no important connection between calprotectin serum levels and the length of AV in their patients. This contrasted with the findings of **Fouda *et al.*** [21], who discovered a strong positive association between serum calprotectin levels and acne duration(r =0.247; P =0.057).

In this study, a ROC curve analysis was run to find a cut-point that can discriminate acne form control subjects. A cutoff value more than 13 µg/ml is a prefect discriminator (AUC =1.000, with 100% sensitivity, and specificity). Our study demonstrated that that serum calprotectin at cutoff value of >17.9 µg/ml can perfectly discriminate moderate from mild cases of acne, serum calprotectin at cutoff value of >19.2 µg/ml can perfectly discriminate severe from moderate cases of acne and serum calprotectin at cutoff value of >17.9 µg/ml can perfectly discriminate sever from mild cases of acne.

Basha *et al.* [20] demonstrated that serum calprotectin concentration with a cutoff point higher than 1.03 (ng/ml) had 77.5% sensitivity, 80% specificity, 79.5% PPV, 78% NPV and accuracy of 78.75% for AV diagnosis. While, for detection of AV severity using mild versus moderate and severe cases, the cutoff point higher than 1.1 (ng/ml) had 96.3% sensitivity, 100% specificity, 100% PPV, 92.8% NPV and accuracy of 97.5%. While, using mild and moderate versus severe cases, the cutoff point higher than 1.22 (ng/ml) had 92.9% sensitivity, 100% specificity, 100% PPV, 96.3% NPV and accuracy of 97.5%. These data showed that serum calprotectin concentration can be a discriminator for the diagnosis of AV and detection of disease severity with high specificity and sensitivity of the test. Likewise, calprotectin can act as an accurate predictor of acne intensity, according to **Abd Allah *et al.*** [19] results, and may aid in the care and follow-up of patients with acne vulgaris.

Farag *et al.* [22] found that acne vulgaris patients could be distinguished from healthy controls with remarkable accuracy (AUC =0.980) when their serum calprotectin levels were compared. They also discovered that calprotectin and calprotectin gene polymorphism should be utilized as a valid predictor of acne severity and may aid in the therapy and follow-up of individuals with acne vulgaris.

STUDY LIMITATIONS

1) Small sample size.
2) There is a need to assess serum levels of calprotectin after systemic treatment to confirm the Calprotectin's Function in the Development of acne.

CONCLUSIONS

Acne vulgaris patients had increased serum calprotectin levels compared to control subjects, and they have a

statistically significant relationship with disease severity, suggesting that calprotectin may be used as a chemical biomarker to determine disease severity. Calprotectin may be a useful marker of acne severity and treatment response based on the results of the current investigation. In addition, calprotectin's likely role in mediating the inflammatory process makes it a desirable therapeutic target for the treatment of acne.

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Conflict of interest: Nil.

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