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Serum Leptin and Adiponectin in Obese and Non-Obese Patients with Acne Vulgaris

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ABSTRACT

Background: Adipokines are demonstrated to be associated with multiple cutaneous diseases. Leptin is mainly produced by the adipocytes that stem from the obese gene. In addition, it was reported that, secretion of leptin is a response to increased lipid uptake, thus, it might be regarded as a link between improper diet and the development of inflammatory acne.

Objective: The aim of the current work was to estimate serum leptin and adiponectin in both obese and non-obese patients with acne vulgaris and to evaluate adiponectin/leptin ratio (A/L) rates as a biomarker of insulin resistance and hence their role in pathogenesis of acne vulgaris in correlation with body weight and disease severity.

Patients and methods: This prospective case-controlled study included a total of 60 patients with acne vulgaris, attending at the Dermatology, Andrology & STD Outpatient Clinic, Mansoura University Hospitals. Forty healthy subjects matched with the patients in age, sex were included. This study was conducted between April 2019 to January 2020.

Results: Cases with acne vulgaris demonstrated significant increase in serum leptin level as well as significant decrease in serum adiponectin level compared to controls. No significant correlation was reported between both serum leptin and adiponectin levels and disease severity. Leptin could be used as reliable predictor in terms of the differentiation between cases of acne vulgaris and controls with high sensitivity, specificity and accuracy. Adiponectin could be used as reliable predictor in terms of the differentiation between cases of acne vulgaris and controls with high sensitivity, specificity and accuracy.

Conclusion: Acne vulgaris was associated with significant elevation in leptin level, significant reduction in adiponectin level and significant decrease in A/L ratio. Thus, leptin, adiponectin and insulin resistance may be pathogenic cofactors contributing to the development of the disease and could be used as reliable predictors for development of acne vulgaris but not for severity of disease.

Keywords: Serum leptin and Adiponectin, Obese and Non-Obese, Acne Vulgaris.

INTRODUCTION

Acne vulgaris is an inflammatory disease of the pilosebaceous unit. The pathogenesis of acne is multifactorial, and adipokines secreted from the sebaceous gland are considered novel factors affecting acne inflammation. Several studies have investigated the association between serum levels of various adipokines and acne vulgaris in patients; however, the results have been inconsistent [(1, 2)].

Adipokines are small molecular weight biologically active proteins primarily produced by adipocytes, however many members are expressed and secreted also by non-adipocyte cells [(3)]. The roles of adipokines in regulating inflammatory responses in adipose tissues and systemic organs become evident during the development of obesity and in response to infection or systemic inflammation. An increasing number of studies have identified the relationship between various adipokines and multiple cutaneous diseases [(4, 5)].

Leptin is mainly produced by the adipocytes that stem from the obese gene. The function of leptin in the sebocyte is to form lipid droplets within the cell. Moreover, leptin can activate the STAT-3 and NF-κB pathways and induce pro-inflammatory enzyme and cytokine (IL-6 and IL-8) secretion in human sebocytes, which suggests that the leptin signaling may be involved in the pro-inflammatory regulation of sebaceous lipid metabolism. Given the fact that secretion of leptin is a response to increased lipid uptake, leptin might be regarded as a link between improper diet and the development of inflammatory acne [(6)].

Adiponectin is an adipocyte-derived hormone that plays a role in insulin function and energy homeostasis. Early studies indicated that adiponectin has an anti-inflammatory effect on endothelial cells by inhibiting the following: nuclear factor κB activation [(7)].

The adiponectin/leptin ratio (A/L) has been suggested as a marker of adipose tissue dysfunction. This emerging biomarker correlates negatively with BMI. Moreover, it is strongly associated with surrogate measures of insulin resistance such as the homeostatic model assessment (HOMA), the hyperinsulinemic-euglycemic clamp and the quantitative insulin sensitivity check index (QUICKI) in different cohorts. Furthermore, it has been stated that the adiponectin/leptin ratio correlates with insulin resistance better than adiponectin or leptin alone, or HOMA even in subjects with hyperglycemia [(8)].

Obesity is characterized by a generalized change in the levels of circulating adipokines due to abnormal accumulation and dysfunction of adipose

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tissue. Altered adipokine levels underlie complications of obesity as well as the increased risk for the development of obesity-related comorbidities such as type 2 diabetes, cardiovascular and neurodegenerative diseases [9].

The aim of the current study was to estimate serum leptin and adiponectin in both obese and non-obese patients with acne vulgaris and evaluate A/L rates as a biomarker of insulin resistance and hence their role in pathogenesis of acne vulgaris in correlation with body weight and disease severity.

PATIENTS AND METHODS

This prospective case-controlled study included a total of 60 patients with acne vulgaris, attending at the Dermatology, Andrology & STD Outpatient Clinic, Mansoura University Hospitals. This study was conducted between April 2019 to January 2020.

The included subjects were divided into two groups;
Group A (patient group) consisted of 60 patients with acne vulgaris who were subdivided into 30 non-obese patients and 30 obese patients, and **Group B (control group)** consisted of 40 healthy subjects matched with the patients in age, sex, and who were subdivided into 20 non-obese persons and 20 obese persons.

Inclusion criteria: 60 patients with acne vulgaris divided in to obese and non-obese patients according to body mass index (BMI) [10].
Exclusion criteria: Patients receiving medications known to affect adipokines level (oral retinoids and hypolipidemic drugs), patient with systemic diseases as diabetes mellitus, renal failure and liver failure, patient with any other systemic inflammatory diseases, and pregnancy and lactation.

All subjects were subjected to:

1. **Full history taking:** A detailed history including (age, duration of disease, presence of any other family member with acne vulgaris, smoking, comorbidities as (liver, renal and cardiac diseases), previous medical history and current treatment.
2. **Complete general and dermatological examination.**
3. **Body mass index (BMI) calculation:** Body mass index was calculated as weight in kilograms divided by height in meters squared and was based on participants' self-reported answer to the following question: "What was your weight and height when last measured?". A BMI of 18.5 to 24.9 is considered normal (non-obese), 25 or higher (overweight), and 30 or higher (obese). We pooled the overweight and obese categories under obese groups.
4. **Determination of Acne vulgaris severity by the Global Acne Grading System [11].**
5. **Assessment of serum leptin and adiponectin:** by using enzyme linked-immunosorbent assay (ELISA) in both patients and controls.

Serum leptin assay:

This Human Leptin ELISA Kit is based on standard sandwich enzyme-linked immunosorbent assay technology. The test samples and the biotinylated Human Leptin specific detection antibody were added to the wells subsequently and then followed by washing the plate. Streptavidin-HRP was added and unbound conjugates were washed away with Wash Buffer. TMB was catalyzed by HRP producing a blue color product that changes into yellow after adding acidic Stop Solution. Leptin amount of sample was captured in plate.

Serum adiponectin assay:

This Human Leptin ELISA Kit is based on standard sandwich enzyme-linked immunosorbent assay technology. Human adiponectin present in the standards/ samples was bound to the capture antibody. The biotinylated goat anti-human adiponectin detection antibody was added to form an Ab-Ag-Ab sandwich. Streptavidin-HRP was added and unbound conjugate was removed with wash Buffer. Next, addition of HRP substrate, TMB, results in the production of a blue colored product that change to yellow after the addition of acidic Stop Solution.

Assessment of adiponectin / leptin ratio: Plasma adiponectin/ leptin ratios have been assessed as biomarkers of systemic insulin resistance.

Ethical considerations:

Written informed consent of all the subjects included in the study was obtained. The research approval was obtained from institutional review board (IRB) of Faculty of Medicine at Mansoura University before starting the study. The researcher clarified the objective and aim of the work to the subjects included in the study. The researcher assured maintaining anonymity and confidentiality of subjects data. Subjects were informed that they allowed to choose to participate or not in the study and that, they had the right to withdraw from the study at any time without giving any reasons. Ethics, values, culture and beliefs of subjects were respected.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

Data were fed to the computer and analyzed using IBM SPSS software package version 22.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. Chi-Square test for comparison of 2 or more groups. Fischer Exact test was used as correction for Chi-Square test when more than 25% of cells have count less than 5 in 2*2tables. Parametric tests: Student

t-test was used to compare 2 independent groups. Non-Parametric tests: Mann-Whitney U test was used to compare 2 independent groups. Wilcoxon signed rank test: was used to compare 2 dependent groups. Receiver Operating Characteristic (ROC) curve analysis: The diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. Sensitivity and Specificity were detected from the curve and PPV, NPV and accuracy were calculated through cross tabulation. P value < 0.05 was considered significant.

RESULTS

There were no statistically significant differences among both groups in terms of age and sex (P>0.05). There were no statistically significant difference among both groups regarding BMI and obesity (P>0.05). There was highly statistically significant increase in serum leptin level among cases compared to controls (P<0.001). There was highly statistically significant decrease in adiponectin level among cases compared to controls (P<0.001) (Table 1).

Table (1): Analysis of demographic data, BMI, state of obesity, serum leptin levels, serum adiponectin levels in the acne vulgaris and control groups:

		Groups				Test of significance
		Acne vulgaris Group (N=60) Mean+ SD N (%)		Control Group (N=40) Mean+ SD N (%)		
Age (years)		22.90 ± 4.20		23.55 ± 3.71		t= 0.733 P = 0.465
Gender	**Male**	14	23.3%	16	40%	$\chi 2$= 3.17 P= 0.07
	Female	46	76.7%	24	60%	
BMI (Kg/m^2)		25.98 ± 5.82		26.67 ± 4.42		t= -0.633 P = 0.528
Obesity	**Non-obese**	30	50 %	20	50 %	$\chi 2$= 0 P= 1
	Obese	30	50 %	20	50 %	
Serum leptin levels (ng/dl)		10.01 ± 1.19		4.07 ± 0.94		z= *-3.973* p < 0.001*
Serum Adiponectin levels (ng/dl)		1.30 ± 0.05		3.42 ± 0.26		z= *-5.801* p < 0.001*

P: probability. Continuous data expressed as mean ± SD.
Categorical data expressed as Number (%) T= independent samples t-test. $\chi 2$= Chi-square test

The mean duration was 3.93 ± 2.85 and the mean Global acne score was 23.48 ± 11.02. In terms of disease severity (GAGS), the majority of cases were mild (43.3%) and moderate (33.3%), while nine cases were severe (15%) and only five cases were very severe (8.3%) (Table 2).

Table (2): Analysis of the disease duration and severity in the acne vulgaris group:

	Cases (N=60)
Duration of the disease (years)	
Mean ± SD	3.93 ± 2.85
Median (min-max)	3 years (5 months- 15 years)
Global acne grading score (GAGS)	
Mean ± SD	23.48 ± 11.02
Median (min-max)	19 (9- 51)
Disease severity (GAGS)	**4.03 ±0.60**
Mild	26 (43.3%)
Moderate	20 (33.3%)
Severe	9 (15%)
Very severe	5 (8.3%)

Continuous data are expressed as mean ± SD/ median (range)
Categorical data are expressed as number (percent %) within group.

There were no statistically significant differences in serum leptin and adiponectin levels among the four studied groups (in other words no significant correlation between both serum leptin and adiponectin levels and disease severity) (P>0.05) (Table 3).

Table (3): Comparison of the serum leptin and adiponectin levels according to disease severity in the acne vulgaris group:

Variable	Mild (N= 26)	Moderate (N= 20)	Severe (N= 9)	Severe (N= 5)	Test of sig.
Leptin (ng/dl)					
mean ± SD	**6.48 ± 0.90**	**11.33 ± 1.21**	**15.82 ± 1.96**	**12.67 ± 3.29**	**KW= *7.159*** **P = 0.*067***
Adiponectin (ng/dl)					
mean ± SD	**1.05 ± 0.28**	**1.11 ± 0.08**	**2.21 ± 0.08**	**1.68 ± 0.08**	**KW= *7.124*** **P = 0.0*68***

P: probability.
Continuous data expressed as mean±SD
KW = Kruskal Wallis test

The analysis of serum leptin and adiponectin levels in obese and non-obese patients with acne vulgaris. There was statistically significant increase in leptin among obese cases compared to non-obese cases (P<0.05), while, there was no significant differences among both groups regarding adiponectin level (P>0.05).

The analysis of serum leptin and adiponectin levels between obese and non-obese (control group). There was statistically significant increase in leptin and significant decrease in adiponectin among obese cases compared to non-obese cases **(P<0.05) (Table 4).**

Table (4): Serum leptin and adiponectin levels between obese and non-obese (patients and control group) with acne vulgaris:

	Acne vulgaris group (N=60)		**Test of significance**
	Non-obese (N=30)	**Obese (N=30)**	
Serum leptin levels			
Mean ± SD	3.37 ± 0.06	16.65 ± 1.17	Z= -*5.902* p < 0.001*
Serum adiponectin levels			
Mean ± SD	1.47 ± 0.6	1.13 ± 0.03	Z= -*0.835* p= 0.*403*
	Control group (N=40)		**Test of significance**
	Non-obese (N=20)	**Obese (N=20)**	
Serum leptin levels			
Mean ± SD	0.95 ± 0.06	7.19 ± .42	Z= -*4.619* p < 0.001*
Serum adiponectin levels			
Mean ± SD	4.03 ± 0.92	2.81 ± 0.51	Z= -*2.110* p= 0.*035**

P: probability. Continuous data expressed as mean±SD and (range)
z= Mann-Whitney u-test
*: Statistically significant (p<0.05)

The predictive ability of leptin to differentiate between cases of acne vulgaris and controls. At cut off > 1.61 (AUC=0.735), leptin could be used as reliable predictor (P<0.001) in terms of the differentiation between cases of acne vulgaris and controls with 80% sensitivity, 60 Specificity, 68.2% PPV, 84,6 NPV and 78% accuracy.

The predictive ability of adiponectin to differentiate between cases of acne vulgaris and controls. At cut off < 1.72 (AUC=0.844), adiponectin could be used as reliable predictor (P<0.001) in terms of the differentiation between cases of acne vulgaris and controls with 83.3% sensitivity, 77.5 Specificity, 72.2% PPV, 88,4 NPV and 80.6% accuracy (Table 5).

Table (5): Predictive ability of leptin and adiponectin to differentiate between cases of acne vulgaris and controls:

	Leptin	Adiponectin
AUC	0.*735*	0.*844*
Cut off point	> ***1.61***	< **1.72**
Sensitivity (%)	**80%**	***83.3*%**
Specificity (%)	***60*%**	**77.5%**
PPV (%)	***68.2*%**	**72.2%**
NPV (%)	***84.6*%**	**88.4%**
Accuracy	***78*%**	**80.6%**
P value	<0.001*	<0.001*

AUC: Area under curve

There was statistically significant higher median adiponectin /leptin ratio among control group than acne vulgaris group (Table 6).

Table (6): Comparison of median adiponectin /leptin ratio between the acne vulgaris and control groups:

	Acne vulgaris group (n=60)	Control group (n=40)	test of significance
Adiponectin/leptin ratio median (min-max)	**0.164 (0.01-7.05)**	**1.725 (0.06-23.22)**	**Z=5.45 P<0.001***

Z:Mann Whitney U test *statistically significant if p<0.05

DISCUSSION

The current study demonstrated that, there were no statistically significant differences among both groups in terms of age and sex. Such fact indicated that both groups were comparable and the demographic features were not interfering with the net results of the study.

Regarding serum leptin levels, the current study demonstrated that, there was highly statistically significant increase in serum leptin level among cases compared to controls. In addition, there was no significant difference among the four studied acne groups (mild, moderate, severe and very severe) regarding serum leptin level.

In harmony with the current study, **Kaymak *et al.*** [(12)] demonstrated that, cases with acne were associated with an increase in leptin level compared to healthy controls (20.44 versus 20.01), however such increase didn't reach the statistical significance.

Similarly, **Ozuguz *et al.*** [(13)] have conducted their study on a total of 30 non obese patients with moderate acne vulgaris, and 15 age-sex compatible controls. They have demonstrated that there was an increase in serum leptin level among acne group in comparison with the control group (8.3±13.6 versus 7.5±14.2) with no statistically significance.

Another recent meta-analysis conducted in 2019 has demonstrated that, there was no significant difference among acne vulgaris cases and the controls in terms of serum leptin level [(2)]. In contrast to the current findings, **Karadag *et al.*** [(14)] reported that basal leptin levels in the acne patients were significantly lower than controls.

The discrepancies among the current sturdy and the previously mentioned studies may be due to the fact that, their patients were non-obese, while the current study had obese and non-obese ones.

Another reasonable explanation may be due to the fact that, their patients had moderate acne vulgaris, while the current study had severe forms in addition to moderate ones which may interfere with the significant elevation in serum leptin level among acne vulgaris cases. Such alteration raises the awareness about the potential role of obesity as well as BMI in acne vulgaris pathogenesis and further researches have to be conducted on large sample size to confirm such outcomes or exclude it.

Regarding serum adiponectin levels, the current study demonstrated that, there was highly statistically significant decrease in serum adiponectin level among cases compared to controls (P<0.001). In addition, there was no significant difference among the four studied acne groups (mild, moderate, severe and very severe) regarding serum adiponectin level.

This came in accordance with **Aydin *et al.*** [(4)] who demonstrated that, patients with acne vulgaris had significantly lower serum adiponectin levels than controls. Similarly, **Çerman *et al.*** [(15)] have conducted their study on a total of 50 patients with acne vulgaris and 36 healthy control subjects. They have displayed that, serum adiponectin levels were significantly lower (P = 0.015) in acne patients than in the controls.

In contrast to the current findings, **Karadag *et al.*** [(14)] reported that basal adiponectin levels were significantly higher compared with the control group. Additionally, **Ozuguz *et al.*** [(13)] reported that, there was no statistically significant difference among non-obese patients acne vulgaris cases and controls groups in terms of adiponectin level.

Comprehensive studies that investigate the numerous adipokines in non-obese and obese acne

patients with their age and sex-matched control groups may reduce uncertainty on this issue [13].

Notably, adiponectin was demonstrated to be associated with anti-inflammatory effects via the inhibition of the mechanistic targets of rapamycin complex 1 signalling [1].

Regarding adiponectin/leptin ratio (A/L), this study demonstrated that, there was statistically significant higher median adiponectin/leptin ratio among controls than patients with acne vulgaris **(P<0.001). Ozuguz *et al.* [13]** demonstrated that, there was no statistically significant difference in adiponectin/leptin ratio between patients with acne vulgaris and healthy controls.

In this study, the mean duration was 3.93 ± 2.85 and the mean Global acne score was 23.48 ± 11.02. In terms of disease severity (GAGS), the majority of cases were mild (43.3%) and moderate (33.3%), while nine cases were severe (15%) and only five cases were very severe (8.3%).

The mean age was 20.60 years and the mean duration of the disease was 2.8 years. All of patients had moderate acne vulgaris (GAGS 19-30) [13].

With regard to the correlation between serum leptin and obesity, the current study revealed that, there was statistically significant increase in serum leptin among obese cases compared to non-obese cases either in cases with acne or acne free ones **(P<0.05).**

Notably, studies have observed that obesity causes high levels of serum leptin, which acts as a pro-inflammatory cytokine and amplifies the process of insulin resistance [16, 17].

This came in accordance with **Ekmen *et al.* [18]** who have demonstrated that, the mean leptin levels were significantly higher in the obese group compared to the non-obese group (2.53 ng/mL versus 1.23 ng/mL; $p < 0.01$). Similarly, **Kumar *et al.* [17]** demonstrated significantly higher levels of serum leptin in obese patients (51.24 ± 18.12) than non-obese patients (9.10 ± 2.99) with p-value < 0.0001.

In addition, **Minocci *et al.* [19]** also reported similar findings that increased BMI was associated with increased leptin levels. These levels were directly proportional to subcutaneous fat and were inversely proportional to abdominal fat index and/or waist-hip ratio.

Concerning the correlation between serum adiponectin and obesity, the current study revealed that, there was statistically significant decrease in serum adiponectin among obese cases compared to non-obese cases among acne free ones only **(P<0.05).** Such outcomes raise the attention about the potential role of adiponectin pathogenesis among acne vulgaris affected cases.

This came in agreement with **Silva *et al.* [20]** who have demonstrated that, adiponectin levels were inversely correlated with obesity and BMI in the general population.

In the same line, **Gariballa *et al.* [21]** demonstrated that, increased visceral fat in overweight and obese subjects was associated with decreased total adiponectin levels. Thus, they recommended that, the health benefits of increasing adiponectin levels using different dietary intervention strategies need to be explored in larger studies.

The current study has demonstrated that serum leptin and serum adiponectin could be used as reliable predictors of acne vulgaris with high sensitivity and specificity. To the best of our knowledge, this was the first study that demonstrated that; serum leptin as well as serum adiponectin could be used as reliable predictors for acne vulgaris development.

CONCLUSION

It could be concluded that acne vulgaris was associated with significant elevation in leptin level, significant reduction in adiponectin level and significant decrease in A/L ratio. Thus, leptin, adiponectin and insulin resistance may be pathogenic cofactors contributing to the development of the disease and could be used as reliable predictors for development of acne vulgaris but not for severity of disease. Additionally, leptin level was demonstrated to be significantly elevated among obese cases either with or without acne, while adiponectin seemed to be significantly decreased among acne free obese subjects only that raise the attention about the potential role of adiponectin in pathogenesis of acne vulgaris disease.

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