BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X

Online ISSN 2357-0016

Original article

Serum Midkine Level in Patients with Acne Vulgaris

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Received:

Accepted:

Abstract

Background: Acne vulgaris (AV) is a chronic inflammatory skin condition that significantly impacts individuals' dermatological health and psychological well-being. Midkine, a pro-inflammatory cytokine, has been implicated in various pathological conditions, but its role in acne vulgaris remains underexplored. **This study aimed to** investigate the serum levels of midkine in AV patients compared to healthy controls and to evaluate the association between midkine levels and the variables of acne vulgaris. **Methods:** This case-control study was executed within the Outpatient Clinic of the Dermatology & Andrology Department, Benha University Hospitals, including 120 individuals categorized into two primary groups: Group I, comprising 60 individuals diagnosed with AV, and Group (II) (control group), included 60 healthy individuals. Serum midkine levels were measured using a double-antibody sandwich ELISA. The clinical severity of acne was assessed with the Global Acne Grading Scale (GAGS). **Results**: There were significantly higher serum midkine levels in acne vulgaris patients (mean ± SD: 397.2 ± 150.3 pg/ml) compared to controls (mean ± SD: 212.5 ± 65.4 pg/ml; $P < 0.001$). No significant correlation was observed between serum midkine levels and acne severity among patients ($P > 0.05$). However, a significant positive correlation was detected between serum midkine levels and BMI ($r=0.559$, $P < 0.001$). **Conclusion:** Our study lends credence to the hypothesis that midkine contributes to the pathogenesis of acne through mechanisms involving the recruitment of inflammatory cells and the induction of chemokine production. These insights highlight the potential of midkine as a biomarker and therapeutic target in acne vulgaris.

Keywords: Acne vulgaris; Midkine; Inflammatory cytokines; Serum levels; Biomarker.

Introduction

Acne vulgaris, an inflammatory affliction of the pilosebaceous unit, primarily targets the facial and trunk areas. It can result in lasting physical scarring, adversely affect an individual's quality of life and self-image, and is associated with elevated rates of anxiety and depression (1).

Acne is caused by hormonal imbalances, bacterial growth, and external factors like diet, pollution, and stress- leading to sebum overproduction, blocked follicles, and inflammation. These interact, causing chronic inflammation in the skin's pilosebaceous units (2).

The intensity of acne is influenced by multiple parameters, such as; the size and type of the lesions, the presence of inflammatory processes, the extent of involvement, and the persistence of scarring. Although topical therapies are commonly utilized, topical and oral pharmacological agents, including topical retinoids, antibiotics, and oral contraceptives- are often prescribed for cases of moderate to severe severity (3).

Midkine, a growth factor, affects cell growth and inflammation and shows elevated levels in conditions like arthritis and obesity. Its roles in the nervous system, cancer, and inflammation suggest it as a potential target for diseases with high midkine levels, though its effects on skin conditions remain under-researched (4).

Studies suggest midkine plays a key role in inflammation, enhancing leukocyte migration, suppressing regulatory T cells, and boosting chemokine production. Its properties promote inflammatory cell recruitment, suggesting its elevated expression in diseases with inflammation (5).

The purpose of this study was to evaluate serum midkine levels in acne vulgaris patients, compare their levels in healthy controls, and correlate them with the disease variables.

Subjects and Methods

Patients:

This case-control study was executed within the Outpatient Clinic of the Dermatology & Andrology Department, Benha University Hospitals, including 120 individuals divided into 2 main groups: Group I, comprising 60 AV patients, and Group II (control group), which included 60 healthy individuals. The study was done over a period of one year from April 2022 to March 2023.

Informed consents were obtained from all participants. Preceding the commencement of the investigation, a pre-study assessment was conducted. No adversities or hazards were discerned throughout the duration of the study. The outcomes derived from this research endeavor were exclusively utilized for scientific inquiry and advancement. Engagement in the study was voluntary,

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with participants exercising their own discretion in participation. This investigation obtained authorization from the Benha Faculty of Medicine's ethics committee for research involving human subjects (Approval number: Ms 28-3-2021).

Inclusion criteria were adult patients ≥18 years old, presenting with diverse levels of severity of AV.

Assessment of Acne Vulgaris Severity: The clinical severity of acne was assessed using the Global Acne Grading Scale (GAGS). This scale evaluates acne severity by summing scores from six areas of the face and trunk, factoring in lesion severity (comedone=1, papule=2, pustule=3, nodule=4) and region-specific multipliers (forehead, cheeks=2; nose, chin=1; chest, back=3), reflecting each area's skin characteristics (6).

Exclusion Criteria: Patients with systemic diseases (such as cardiac diseases), other inflammatory diseases (including asthma and inflammatory bowel disease) (7), autoimmune diseases (such as rheumatoid arthritis and systemic lupus erythematosus), and malignancies (including esophageal cancer, oral cancer, neuroblastoma, and hepatocellular carcinoma) (8, 9)- were excluded from the study.

All participants in the study underwent the following:

Detailed history including personal details (age, name, gender), the onset, progression, and duration of the disease, any family history of AV, and a record of previous treatments, both systemic and topical.

Full Clinical examination:

General examination to exclude systemic diseases. **Local examination** using the global acne grading scale (GAGS), which evaluates acne severity by summing scores from six areas, factoring in lesion severity (comedone=1, papule=2, pustule=3, nodule=4) and region-specific multipliers (forehead, cheeks=2; nose, chin=1; chest, back=3), reflecting each area's skin characteristics (10).

Laboratory tests

Serum sample collection and storage: Fasting venous blood samples (5 ml) were collected from both patients and controls, allowed to clot at room temperature in sterile conditions, and then refrigerated. Post-clotting, the samples were centrifuged for 15 minutes at 2000-3000 rpm to separate the serum, which was immediately stored at -20°C. These serum samples were later used to measure midkine levels.

Determination of serum midkine: A commercial human serum midkine ELISA kit for research use only (Cat #: 201-12-0799, HuTai Road, Baoshan District, Shanghai, China). A double antibody sandwich ELISA (Enzyme-Linked Immunosorbent Assay) was used to detect serum levels of Midkine.

Test principle: A double-antibody sandwich ELISA was used to assay human midkine levels. midkine samples were incubated in wells pre-coated with monoclonal antibodies, followed by the addition of biotin-labeled antibodies and Streptavidin-HRP to form an immune complex. After washing away unbound enzymes, Chromogen Solutions A and B were added, causing a color shift to blue and then yellow under acidic conditions. The intensity of the yellow indicates the midkine concentration.

Assay procedure: The ELISA test process began with standard reagent dilution as per instructions. Plate quantities were based on the sample and standard amounts, and duplicates were recommended for each standard and blank well. Blank wells excluded samples and antibodies, using only chromogen solutions and stop solutions. Standard wells received standard and Streptavidin-HRP, avoiding extra antibodies due to pre-combined biotin. Test wells included samples, Midkine-antibody, and Streptavidin-HRP, followed by incubation. Washing involved diluted concentrate and careful membrane handling. Chromogen solutions were then added, mixed, and incubated away from light. The reaction was halted with a stop solution, turning the solution yellow. OD was measured at 450 nm, using the blank as a baseline. A standard curve determined sample concentrations from their OD values.

Statistical analysis

Data was collected and analyzed using Microsoft Excel 2016 and IBM SPSS version 26 (IBM, Armonk, New York, United States). The Kolmogorov-Smirnov test checked data normality. Descriptive statistics included means and standard deviations for parametric data and medians and ranges for non-parametric data, along with frequencies and percentages for qualitative data. Analytical methods featured the student t-test, Mann-Whitney Test, Kruskal-Wallis test, and Chi-Square test for various comparisons, with Fisher's exact test for small expected counts. Correlation analysis and ROC Curves assessed the relationship strength between variables and diagnostic measure accuracy, respectively, with significance considered at p-values less than 0.05 or highly significant at less than 0.001.

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Results

The present study was conducted on 120 individuals, referred to the outpatient Clinic of the Dermatology & Andrology Department at Benha University Hospitals. They were divided into two main groups. Group I included 60 acne vulgaris patients, and Group II (control group) included 60 healthy individuals.

There was no statistically significant difference between patients and control groups regarding age and gender (P >0.05). Also, there was no statistically significant difference between the two groups regarding occupation (P >0.05). Also, there was no statistically

significant difference in BMI in AV patients when compared to controls (P <0.05), **Table (1).**

More than half of the patients (51.7%) had a mild grade of acne vulgaris. Scar was reported in 25 (41.7%) patients, with the most common type being the ice picks and mixed ice picks + Rolling + Box car in 11 patients (18.3%). Post-inflammatory hyperpigmentation (PIH) was observed in 32 (53.3%) patients, with the most common site being the face in all patients (100%), followed by the back (one-third of patients) and then the shoulder in 31.9%. The upper limb was affected in only one case. The mean duration of the condition was 7.13 months, with a range spanning from 1 month to 18 months, **Table (2).**

There was a statistically significant increase in serum midkine levels in patients compared to controls (P <0.001), **Figure (1).**

The mean serum midkine in patients with mild grade was 327.13± 104.84 pg/ml, 411.86± 213.09 in moderate grade, while the mean serum midkine in patients with severe grade was 453.25± 165.16 pg/ml. There was no statistically significant relation between serum midkine and disease grade among AV patients (p >0.05), **Figure (2).**

There was a statistically significant difference between mild and severe grades regarding serum midkine (P =0.032). Serum midkine was significantly higher in severe cases than in mild cases. There was no statistically significant difference between moderate and severe grades regarding serum midkine (P >0.05), **Figure (3).**

There was no statistically significant relation between serum midkine with gender and occupation among AV patients (P >0.05). Also, the mean serum midkine in AV patients with the scar was 417.6± 207.45 pg/ml, while the mean serum midkine in AV patients with PIH was 380.38± 188.26 pg/ml. There was an absence of a statistically significant correlation between serum midkine concentrations and the occurrence of scarring and PIH among individuals afflicted with acne vulgaris (P >0.05), **Table (3).**

The mean serum midkine in AV patients with PCO was 371.00± 126.87 pg/ml, while the mean serum midkine in AV patients with menstrual irregularity was 380.54± 154.64 pg/ml. In patients with a positive family history, the mean was 375.77± 154.84 pg/ml. No statistically significant disparities were observed in serum midkine levels based on the presence of PCO syndrome, menstrual irregularities, or familial history among individuals with AV (P >0.05), **Table (4).**

There was a significant positive correlation between serum midkine and BMI among the studied patients (r=0.559, P <0.001). In contrast, there was no significant correlation between serum midkine and age and duration of disease (P >0.05), **Figure (4).**

Using ROC-curve analysis, serum midkine levels can significantly determine patients with acne vulgaris with high specificity and sensitivity of 81.8% and 100% in respective manner, when the cutoff point was >131 pg/ml., **Figure (5).**

Table (1): Socio-demographic characters of the studied groups.

Variable		AV Patients (N=60)		Controls (N=60)		Test value	P-value	Sig.
		No.	%	No.	%			
Gender	Male	31	51.7%	31	51.7%	X^2= 0.0	1.00	NS
	Female	29	48.3%	29	48.3%			
Age (years)	Mean± SD	22.23± 4.54		23.68± 5.03		Z_{MWU}=	0.095	NS
	Median (IQR)	21.0 (19.0 – 24.5)		22.5 (20.0 - 27.0)		1.669		
	Range	15.0 - 33.0		15.0 - 37.0				
Occupation	Employee	17	28.3%	19	31.7%	X^2=	0.886	NS
	Worker	12	20.0%	14	23.3%	0.646		
	Housewife	8	13.3%	8	13.3%			
	Student	23	38.3%	19	31.7%			
BMI (Kg/m2)	Mean± SD	23.97± 1.79		23.97± 1.79		Z_{MWU} =	0.229	NS
	Median (IQR)	23.95 (22.3-25.2)		23.6 (22.3-24.3)		1.202		
	`Range	21.2- 31.2		20.6- 31.3				

P value< 0.05 was significant, SD: Standard deviation, ZMWU = Mann- Whitney U test, X^2= Chi- Square test

Table (2): Clinical findings among the studied AV group**.**

Variables		AV patients (No=60)	
		No.	%
Acne grade	Mild	31	51.7%
	Moderate	21	35.0%
	Severe	8	13.3%
Scar	No	35	58.3%
	Yes	25	41.7%

Scar type (n=25)	Ice picks	11	18.3%
	Rolling	3	5.0%
	Ice picks+ Rolling+Box car (combined)	11	18.3%
PIH	No	28	46.7%
	Yes	32	53.3%
Distribution *	Face	60	100.0%
	Chest	15	25.0%
	Shoulder	19	31.9%
	Upper back	20	33.3%
	Upper limb	1	1.7%
Disease duration (months)	Mean± SD	7.13± 4.24	
	Median (IQR)	6.0 (4.0- 8.5)	
	Range	1.0– 18.0	

* More than one site may be found in same patients, PIH: Post inflammatory hyperpigmentation

Table (3): Relation between serum midkine levels with gender, occupation and disease complications among AV patients.

Variable		**Serum midkine (pg/ml)**							**Test value**	**P-value**	**Sig.**
		Mean	**SD**	**Median**	**IQR**		**Range**				
Gender	Male	369.90	167.88	350.00	248.0	460.0	148.0	1026.0	Z_{MWU} = 0.325	0.745	NS
	Female	377.55	161.57	298.00	260.0	444.0	151.0	750.0			
Occupation	Employee	393.29	169.79	430.00	250.0	467.0	151.0	750.0	KW= 0.503	0.918	NS
	Worker	346.08	132.84	314.50	258.5	434.5	148.0	610.0			
	Housewife	378.38	190.64	293.00	264.5	458.0	253.0	743.0			
	Student	371.74	172.10	356.00	250.0	409.0	204.0	1026.0			
Scar	No	342.17	116.5	298.00	253.0	426.0	148.0	630.0	Z_{MWU} = 0.937	0.349	NS
	Yes	417.6	207.45	350.00	260.0	512.0	207.0	1026.0			
PIH	No	365.86	132.71	368.50	255.0	467.0	148.0	630.0	Z_{MWU} = 0.104	0.917	NS
	Yes	380.38	188.26	297.00	262.0	437.0	151.0	1026.0			

P value< 0.05 is significant, SD: Standard deviation, ZMWU = Mann- Whitney U test, KW= Kruskal-Wallis Test

Table (4): Serum midkine levels according to PCO, menstrual irregularities and family history among AV patients.

Variable		Serum midkine (pg/ml)							Test value	P-value	Sig.
		Mean	SD	Median	IQR		Range				
PCO	No	374.47	175.28	298.0	250.0	460.0	148.0	1026.0	z_{MWU} =	0.695	NS
	Yes	371.00	126.87	356.0	271.0	430.0	218.0	630.0	0.393		
Menstrual irregularies	No	368.29	172.09	297.0	250.0	460.0	148.0	1026.0	z_{MWU} =	0.704	NS
	Yes	380.54	154.64	361.50	269.0	430.0	207.0	750.0	0.380		
Family History	Negative	368.12	188.68	351.0	269.0	409.0	151.0	1026.0	z_{MWU} =	0.793	NS
	Positive	375.77	154.84	298.0	250.0	467.0	148.0	750.0	0.263		

P value< 0.05 is significant, SD: Standard deviation, ZMWU = Mann- Whitney U test,

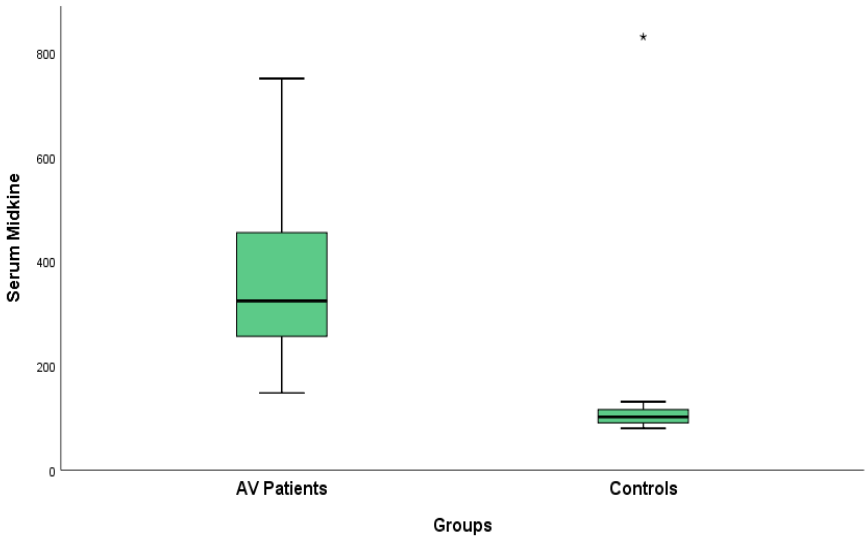

Figure (1): Boxplot showing comparison between AV patients and controls groups regarding serum Midkine.

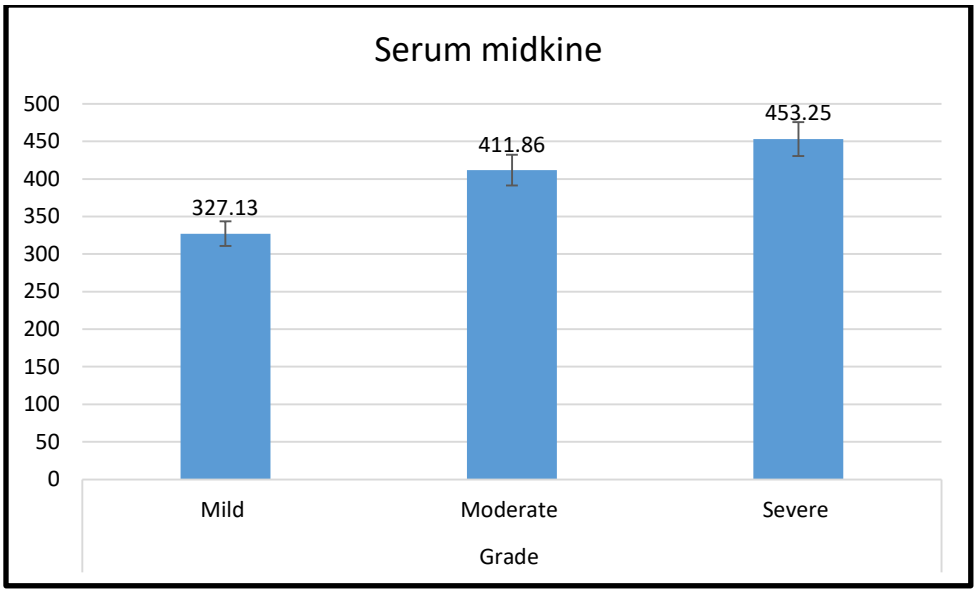

Figure (2): Relation between serum midkine with disease grade among AV patients**.**

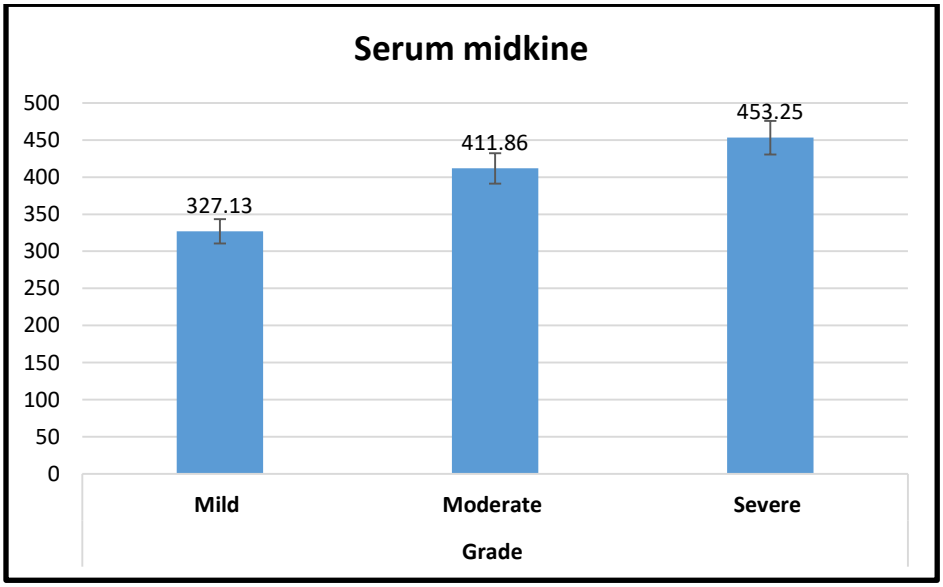

Figure (3): Relation between serum midkine with disease grade among AV patients**.**

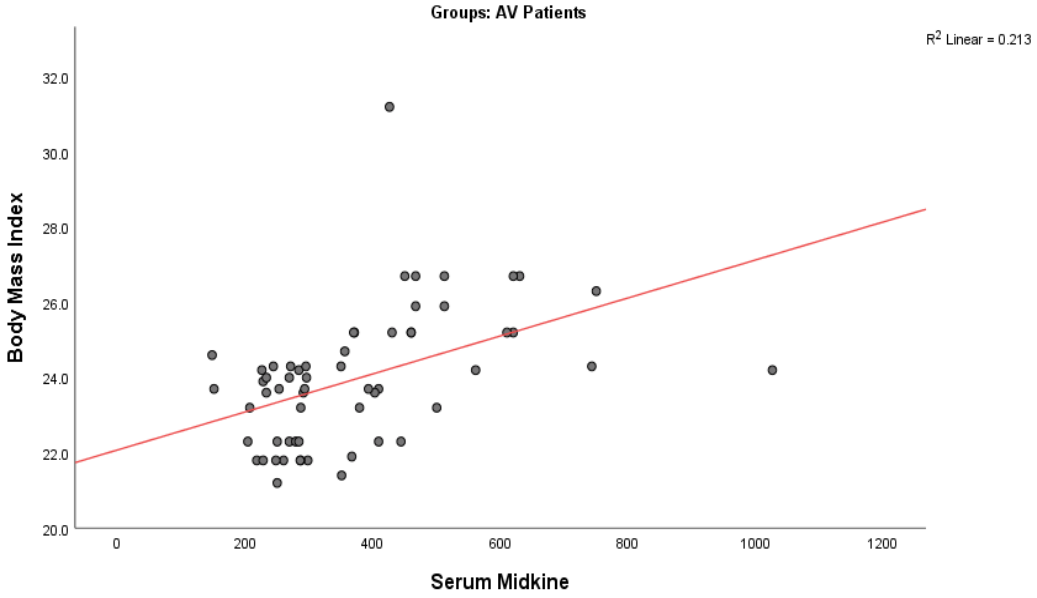

Figure (4): Scatter plot showing significant positive correlation between serum midkine and Body Mass Index.

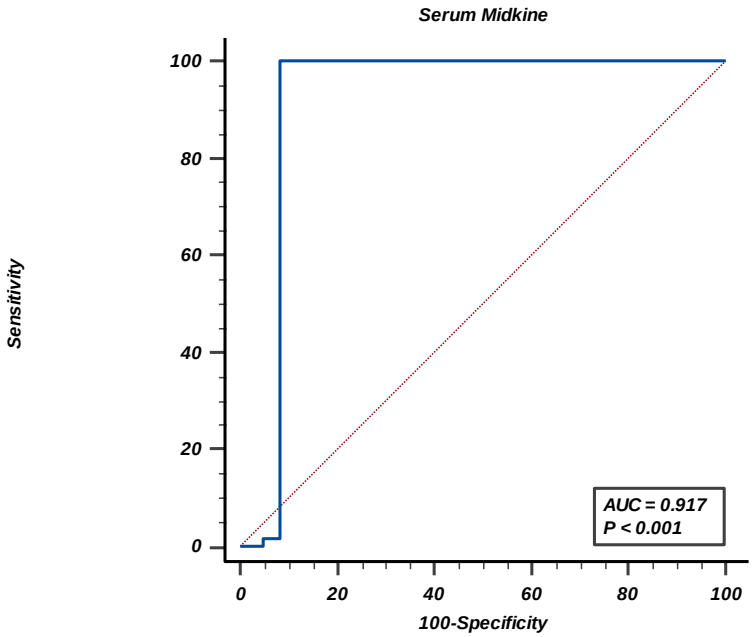

Figure (5): ROC curve for the performance of serum midkine levels in early diagnosis of acne vulgaris.

Discussion:

Acne vulgaris, a prevalent inflammatory skin condition, affects individuals' physical appearance and psychological health, potentially leading to scarring and increased rates of anxiety and depression. The disease's complex etiology involves hormonal fluctuations, bacterial involvement, and environmental factors, leading to inflammation and sebum overproduction. Midkine (MK)- a growth factor linked to various inflammatory diseases- has not been extensively studied in acne vulgaris (11). This research aims to assess serum MK levels in acne patients versus healthy controls, exploring its association with acne severity and potential as a therapeutic target. This case-control study included 120 participants who were divided into; 60 AV patients and 60 controls. The study involved detailed clinical assessments using the global acne grading scale (GAGS) and serum MK level measurement via a double-antibody sandwich ELISA.

To the best of our knowledge, this is the first study to compare MK serum levels in AV patients with healthy controls. On comparison of serum midkine levels between patients and control groups, there was a high statistically significant increase in serum midkine levels in patients when compared to controls compared to controls ($P < 0.001$).

A research endeavor scrutinized the expression patterns of MK in various inflammatory disorders, encompassing psoriasis vulgaris, warts, pustulosis palmoplantaris, and lichen planus. The outcomes insinuate a conceivable linkage between MK expression and keratinization phenomena, albeit not with cellular proliferation, given that keratinocyte proliferation is characteristically attenuated in lichen planus (12).

In the context of inflammatory conditions affecting dermal and subcutaneous tissues, such as Behçet's disease, Henoch–Schönlein purpura, and erythema induratum of Bazin- research has revealed that leukocytes exhibited a pronouncedly positive staining for MK. Conversely, other infiltrating cell types, such as lymphocytes, histiocytes, and leukocytes, demonstrated negative staining (12). MK has been hypothesized to serve as a pivotal mediator in regulating inflammatory responses occurring within the dermal layers of the skin. This finding concurs with a prior report indicating that MK possesses the capacity to induce leukocyte migration (13).

The complexities surrounding the mechanisms underlying the induction of inflammation in acne are profound. Human sebocytes possess functional receptors for platelet-activating factor, which play a role in modulating inflammatory mediators such as COX2, prostaglandin E2 (PGE2), and IL8. Cutibacterium acnes (C. acnes) downregulates histone deacetylase

(HDAC) expression, initiates p38 mitogen-activated protein kinase (MAPK) activation, amplifies the cytokine response through toll-like receptor 2 (TLR2), leading to a significant augmentation of macrophage-activating lipopeptide-2 (MALP2)-induced production of IL1β, IL8, IL6, and CXCL10 in human sebocytes (14).

Sebocytes engage in cutaneous inflammation by attracting and interacting with specialized immune system constituents, a mechanism that precipitates the differentiation and generation of Th17 cells. This evidence suggests a plausible intersectionality in the activation of pro-inflammatory cascades among various inflammatory dermatological conditions, notably including psoriasis and hidradenitis suppurativa (15).

An investigation has demonstrated that subjects afflicted with Hidradenitis suppurativa (HS) possess significantly augmented serum concentrations of midkine (MK), potentially correlating with autoinflammatory phenomena, angiogenic activity, atherogenesis, and an elevated susceptibility to metabolic syndrome (16).

Eliminating midkine had the effect of dampening the symptoms of the animal model of multiple sclerosis, known as experimental autoimmune encephalomyelitis. This was accomplished by enhancing the population of regulatory T cells while simultaneously reducing the numbers of Th17 and Th1 cells. In individuals with RA, there was a positive correlation between serum MK concentrations and IL-17 levels (17).

Furthermore, an investigation revealed that serum concentrations of MK were significantly elevated in individuals diagnosed with psoriasis in comparison to the control cohort (4).

In the year 2014, a study elucidated that MK is present in adipose cells, contributing to the disturbance of insulin signaling pathways in these cells. It was also noted that serum concentrations of MK were heightened in individuals exhibiting obesity (18). Presently, MK is viewed as a prospective therapeutic target for the management of insulin resistance and assorted inflammatory disorders (19).

Midkine serves as a pro-inflammatory cytokine, contributing to the perpetuation of chronic inflammation by enhancing the chemotactic migration and tissue infiltration of neutrophils and macrophages. Additionally, MK has been implicated in the upregulation of the production of a variety of inflammatory mediators, such as IL-8 and IL-6. Numerous studies have provided substantial evidence of MK's role in the onset and progression of autoimmune rheumatic disorders, encompassing SLE, SS, RA, and other autoimmune conditions, such as MS (20).

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Executes this role via two primary pathways; the first entails the chemotactic movement of neutrophils and macrophages, as well as the inhibition of regulatory T cell expansion, while the second is marked by its fibrinolytic capability, which results in the disintegration of basement membranes, thus facilitating the passage of leukocytes from the circulatory system into the tissues. These mechanisms elucidate the pathological importance of MK in the early stages of tissue inflammation (21).

Within the confines of the contemporary investigation, it was discerned that the median level of serum MK among individuals afflicted with severe acne surpassed that observed among those categorized with moderate and mild grades of the condition, with respective values of 453.25, 411.86, and 327.13.

The higher median serum midkine levels observed in patients with severe acne compared to those with moderate and mild grades suggest a correlation between midkine concentration and acne severity. Midkine, involved in inflammation, may escalate the severity of acne by promoting immune cell recruitment and chemokine synthesis. This implies that midkine not only reflects the inflammatory status of acne but might also contribute to its progression, making it a potential target for therapeutic intervention in severe acne cases. Further research is essential to confirm these roles and explore midkine-targeted treatments.

Regarding clinical findings, more than half of the patients (51.7%) had a mild grade of acne vulgaris. Scars were reported in 25 patients (41.7%), with the most common type being ice picks and mixed ice picks Rolling + Box car in 11 patients (18.3%). Post-inflammatory hyperpigmentation (PIH) was observed in 32 patients (53.3%), with the most common site being the face in all patients (100%), followed by the back in a third of patients and then the shoulder in 31.9%. The upper limb was affected in only one case.

These findings corroborate a study's observations highlighting the predominant occurrence of ice-pick scars in 94% of cases following acne, succeeded by rolling scars in 86%, boxcar scars in 54%, and keloidal scars in 10% of the surveyed patient cohort (22).

In terms of affected sites, a study revealed that facial acne as a singularly involved site was the most prevalent type, occurring in 60% of cases. Conversely, multiple site involvement, encompassing the face, chest, and back concurrently- was observed in 37% of cases (23). Furthermore, it was observed that acne predominantly manifested on the facial region in 82.5% of cases, with the back (34.8%) and chest (14.8%) being less commonly affected areas. Among the cohort of acne-afflicted individuals, 71.1% exhibited scarring, while 61.1% experienced PIH (24).

In the current study, PCO was reported in 15 (25%) patients, while menstrual irregularity was found in 26 (43.3%) patients. None of the studied patients had a history of other diseases or medications. Most patients (71.7%) had a positive family history of acne vulgaris. Regarding previous treatment, most cases (86.7%) used topical antibiotics alone or with systemic antibiotics.

Likewise, within the spectrum of cutaneous manifestations discerned in PCOS patients, acne vulgaris emerged as the predominant feature, affecting 67.5% of individuals, closely trailed by hirsutism, which manifested in 62.5% of the cohort (25).

In accordance with our study, two studies found that a family history of acne was significantly more frequent in subjects with acne than in healthy subjects (26, 27).

In the current study, there was no statistically significant relation between serum MK and PCO, menstrual irregularity, or family history among AV patients. Similarly, a study found no statistically significant difference between PCOS patients and controls with regard to serum MK levels (28).

Within RA patients, a study unearthed a correlation between MK levels and several clinical markers, including the Disease Activity Score (DAS)-28, the disability index via the Health Assessment Questionnaire, rheumatoid factor levels and ESR (8).

In contradistinction, a scholarly inquiry unveiled the dearth of a substantive association between the serum concentrations of MK and the severity of psoriasis, as gauged by the PASI scoring paradigm (4).

A notable lack of statistically significant coherence was discerned between the severity of acne and serum levels of MK within the patient population, as evidenced by a p-value surpassing the threshold of 0.05. Nevertheless, an appreciable positive correlation was discerned between serum levels of MK and BMI, evidenced by a correlation coefficient of 0.559 and a p-value less than 0.001.

Our study results were parallel to research that found that BMI has a significant positive correlation with MK level (29). Furthermore, an investigation elucidated that within the cohort of women diagnosed with PCOS, those classified as overweight or obese (BMI ≥25 kg/m²) exhibited markedly heightened levels of MK in comparison to their counterparts categorized as having a normal weight and diagnosed with PCOS (28). Furthermore, an investigation unveiled a discernible positive coherence between the serum concentration of MK and BMI, indicating a relationship of direct proportionality between these two parameters (18).

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This study had some limitations, including the small sample size, which may not fully represent the entire population of patients with AV. Also, the study utilized an observational design. Longitudinal studies would offer a better understanding of the dynamic changes in MK levels over time.

Conclusion:

We can conclude that our study lends credence to the hypothesis that midkine contributes to the pathogenesis of acne through mechanisms involving the recruitment of inflammatory cells and the induction of chemokine production. While these insights highlight the potential of MK as a biomarker and therapeutic target in AV, additional extensive investigations are indispensable to authenticate these discoveries and unravel the therapeutic ramifications of manipulating MK activity in the clinical treatment of this dermatological condition.

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To cite this article: Neveen E. Sorour , Rana A. Khashaba , Fatma A. Attallah, Doaa M. Elhabak. Serum Midkine Level in Patients with Acne Vulgaris. BMFJ XXX, DOI: 10.21608/bmfj.2025.288090.2076