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original article

Evaluation of Serum Survivin level in Patients with Acne Vulgaris

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Abstract

Background: Survivin is a member of the inhibitor of an apoptosis protein family that has been shown to inhibit apoptosis, promote cell proliferation and enhance angiogenesis. It could play potential roles in the pathogenesis of active AV and more importantly in post inflammatory acne scars with significant positive correlation coefficient between serum levels of survivin which support PI3K-/AKT-mediated downregulation of nuclear expression of Fox O transcription factors resulting in enhanced survivin expression. **Aim:** The current study aimed to assess and correlate serum levels of survivin in patients with different degrees of acne and it's relation to severity in comparison to healthy controls. **Method:** This is a case-control study performed on sixty patients with acne vulgaris divided into two groups: the first group included 30 patients suffering from mild acne; the second group included 30 patients suffering from severe acne and acne scars and a third group of 25 sex matched healthy controls were investigated for serum zinc level and compared serum survivin were estimated using commercially available ELISA kits. **Conclusion:** Our findings suggest that, survivin is associated with the susceptibility of development of AV and has a role in its pathogenesis and severity and post inflammatory acne scars.

Key words: acne vulgaris, acne scars, survivin.

Introduction

Acne vulgaris is an inflammatory disorder of pilosebaceous unit, which runs a chronic course and it is self-limiting. It is triggered by Propionibacterium acnes in adolescence, under the influence of normal circulating dehydroepiandrosterone (DHEA). It is a very common skin disorder which can present with inflammatory and non-inflammatory lesions chiefly on the face but can also occur on the upper arms, trunk and back [1].

Microcomedone is the earliest subclinical 'lesion' in acne that may change into open and closed comedones and into different inflammatory lesions, such as papules, pustules, nodules and cysts [2].

Acne pathophysiology includes hyperseborrhoea, abnormal follicular keratinization and Propionibacterium acnes proliferation in the pilosebaceous unit [3].

Causes of acne include (Use of medications like lithium, steroids and anticonvulsant- exposure to excess sunlight - use of occlusive wear like shoulder pads, headbands backpacks - endocrine disorders like polycystic ovarian syndrome and even pregnancy) [4]. During puberty, alteration of the sebaceous lipid profile, called dys-seborrhoea, stress, irritation, cosmetics and potential dietary factors lead to inflammation and formation of different types of acne lesions [3].

Possible outcomes of the inflammatory acne lesions are acne scars which, although they can be treated in a number of ways, may have a negative psychological impact on social life and relationships. The main types of acne scars are atrophic and hypertrophic scars [5].

Acne scars are the direct result of deep trauma to the skin related to acne. External factors, such as picking, can traumatize even small acne lesions and result in scarring. Acne scars manifest as areas of pitted or raised skin and can occur on the face or body. Not to be confused with post acne erythema (redness) or hyperpigmentation (brown spots) which are flat, temporary changes related to inflammation that tend to resolve over time, acne scarring changes the overall texture of the skin and does not always improve with time [6].

Acne may appear in adolescence and it persists through the early thirties. Acne is more common in males than in females. Urban populations are more affected than rural populations. About 20% of the affected

individuals develop severe acne which results in scarring [7].

Survivin is a member of the inhibitor of an apoptosis protein family that has been shown to inhibit apoptosis, promote cell proliferation and enhance angiogenesis [8]. The expression of survivin is undetectable or is found at very low levels in normal tissues, whereas it is found at relatively higher levels in various malignant tissues, embryonic and fetal tissues, and also few normal adult tissues, including skin [9]. In human skin, survivin function has long remained unclear because of several works showing the absence of survivin in human adult epidermis. However, more reports have shown that survivin is indeed expressed in normal human skin, and it is localized in the cytoplasm of a few cells located in the basal layer of the epidermis [10].

Survivin plays potential roles in the pathogenesis of active acne vulgaris and more importantly in post inflammatory acne scars with significant positive correlation coefficient between serum levels of survivin which support PI3K-/AKT-mediated downregulation of nuclear expression of FoxO transcription factors resulting in enhanced survivin expression [11].

As regard to assessment of survivin level in diseases other than AV. Survivin-overexpressing cells were detected in the SSc dermis frequently. The positive rate of survivin in SSc dermis (64.3 %, 9/14) was higher than that in non-SSc dermis (11.2 %, 1/9) [12]. Also another author illustrated that, there was an increase of survivin expression in SSc fibroblasts, leading to apoptosis resistance through survivin anti-apoptotic pathways and TGF-β signaling. So, increased SSc fibroblasts resistance to apoptosis has been associated with excessive fibrosis. This may justify the role of survivin in formation of acne scar [13]. Therefore, additional studies on the expression and subcellular localization of survivin in relation to function will confirm its key role in the skin and will open the field to new therapeutic strategies for many cutaneous conditions such as acne scaring.

Materials and Methods

The Study Population

This is a case-control study .The current study had been conducted between January 2019 and May 2019 after the approval by Research Committee at Faculty of Medicine, Benha University. The study included 85 subjects that were randomly selected from those attending the Dermatology Outpatient's

Clinic at Benha University Hospital, Faculty of Medicine, Benha University, Qalyobia, Egypt. Prior to initiation of the study, every subject was informed about the aim of the study and an informed consent was obtained from each individual before sample collection. They were classified into three groups; the first group included 30 patients suffering from mild acne; the second group included 30 patients suffering from severe acne and acne scars with no history of receiving any treatment for 4 weeks, any systemic disease other than the skin disease, any skin disease other than acne, fibrotic disease as liver cirrhosis, any systemic and topical therapy at least 4 weeks before the study.and the third group consisted of 25 healthy subjects to serve as a control group.

ELISA Assays of IGF-I and Survivin

Quantitative determinations of serum survivin were achieved using a double-antibody sand wich Enzyme Linked Immune Sorbent Assay technique (ELISA) was used to detect serum level of survivin using a commercial Human survivin ELISA Kit for research use only (Cat #: 201-12-8108, SunRedBio, China).

Statistical Analysis

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Student T Test was used to assess the statistical significance of the difference between two study group means.For the comparison of the three groups' means, one way analysis of variance (ANOVA) was used. Chi-Square test was used to examine the relationship between two qualitative variables. Fisher's exact test: was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. Correlation analysis: To assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. p is significant if <0.05 at confidence interval 95%.

Results

The Study Population

The current study is a case control study included 60 patients (19 males and 41 females). The average age of acne vulgaris patients was 21.1±4.1years. Male patients represented 31.7%, while females represented 68.3%. Those patients were divided into two groups; the first group included 30 patients (9 males and 21 females) suffering from mild acne with average age of 21.3±3.4 years. The second group included 30 patients (10 males and 20 females) suffering from severe acne and post inflammatory acne scars with average age of 21.0±3.8 years. Mean disease duration was 3.5 years. All patients had gradual onset, progressive course. Face was affected in100% of cases, back in 51.7%, chest in 26.7%, table (1). The study included another third group consisting of 25 healthy age and sex matched subjects (13 males and 12females) to serve as a control group with an average age 21.1±4.1 years.

Severe cases had significantly higher frequency of back affection and higher GAG score when compared to mild cases. Scar was present in severe cases only (fig 1).

Acne Vulgaris (total and severe cases) had significantly higher frequency of excess sun exposure and stress when compared to control group. Severe AV cases had significantly higher frequency of excess sun exposure when compared to mild AV cases. No significant differences were found in family history, smoking, sun exposure, fat diet between all studied groups. (Table 2)

Biochemical Assessments of Survivin

Mean Survivin in control group was 165.9 ng/mL, while it was 360.2 ng/mL in Acne Vulgaris cases. Acne Vulgaris (total, mild, severe) groups showed significantly higher Survivin when compared to control group ($p<0.001$ for each). In addition, severe cases had higher surviving level when compared to mild cases ($p<0.001$).(table 3 and fig 2)

No significant differences were found in Survivin concentration between scar types in severe acne vulgaris group. Table (4)

Table (1): Comparison of clinical data between all studied cases.

			Total AV	Mild AV	Severe AV	*P*
			N=60	**N=30**	**N=30**	
Duration (years)		**Mean**	3.5	3.5	3.5	0.997[T]
		±SD	±1.1	±0.9	±0.8	
Onset	**Gradual**	**N**	60	30	30	-
		%	100%	100%	100%	
Course	**progressive**	**N**	60	30	30	-
		%	100%	100%	100%	
Site of	**Face**	**N**	60	30	30	-
affection		**%**	100.0%	100.0%	100%	
	Back	**N**	31	6	21	**<0.001**[C]
		%	51.7%	20.0%	70%	
	Chest	**N**	16	5	11	0.080[C]
		%	26.7%	16.7%	37%	
GAG score		**Mean**	22.9	11.1	34.5	**<0.001**[T]
		±SD	±6.3	±2.8	±1.1	
Presence of Scar		**N**	30	0	30	**<0.001**[C]
		%	50%	0%	100%	

SD, standard deviation; T, Student t test; C, chi square.

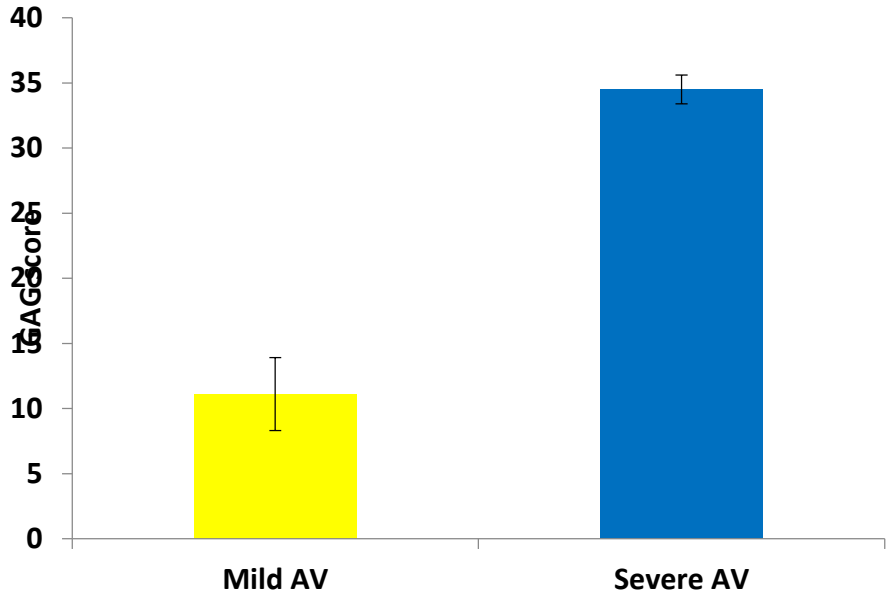

Figure (1): GAG score in mild and severe cases.

Table (2): Comparison of risk factors between all studied groups.

	Control N=30		Acne Vulgaris					
			Total AV N=60		Mild AV N=30		Severe AV N=30	
	N	%	N	%	N	%	N	%
Positive family history	10	40%	29	48.3%	16	53.3%	13	43.3%
***P*¹**	-		0.482^{C}		0.324^{C}		0.803^{C}	
***P*²**	-		-		0.438^{C}			
Smoking	2	8%	10	16.7%	5	16.7%	5	16.7%
***P*¹**	-		0.496^{F}		0.436^{F}		0.436^{F}	
***P*²**	-		-		1.000^{C}			
Excess sun exposure	14	56%	47	78.3%	20	66.7%	27	90.0%
***P*¹**	-		**0.037^{C}**		0.418^{C}		**0.004^{C}**	
***P*²**	-		-		**0.028^{C}**			
high fat diet	5	20%	22	36.7%	12	40.0%	10	33.3%
***P*¹**	-		0.133^{C}		0.110^{C}		0.296^{C}	
***P*²**	-		-		0.592^{C}			
Excess stress	13	52%	49	81.7%	23	76.7%	26	86.7%
***P*¹**	-		**0.005^{C}**		0.055^{C}		**0.005^{C}**	
***P*²**	-		-		0.317^{C}			

C, chi square; F, Fisher exact test.

Table (3): Comparison of Survivin level between all studied groups.

		Control N=30	Acne Vulgaris Total AV N=60	Mild AV N=30	Severe AV N=30
Survivin (ng/mL)	**Mean**	165.9	360.2	302.1	418.3
	± SD	±51.3	±105.8	±99.6	±91.8
	Minimum	19.6	132.4	132.4	159.2
	Maximum	354.2	571.9	487.1	571.9
	***P*¹**	-	**<0.001^{T}**	**<0.001^{T}**	**<0.001^{T}**
	***P*²**	-		**<0.001^{T}**	

SD, standard deviation; T, Student t test; C, chi square.p1, comparison versus control; p2, comparison between mild and severe cases.

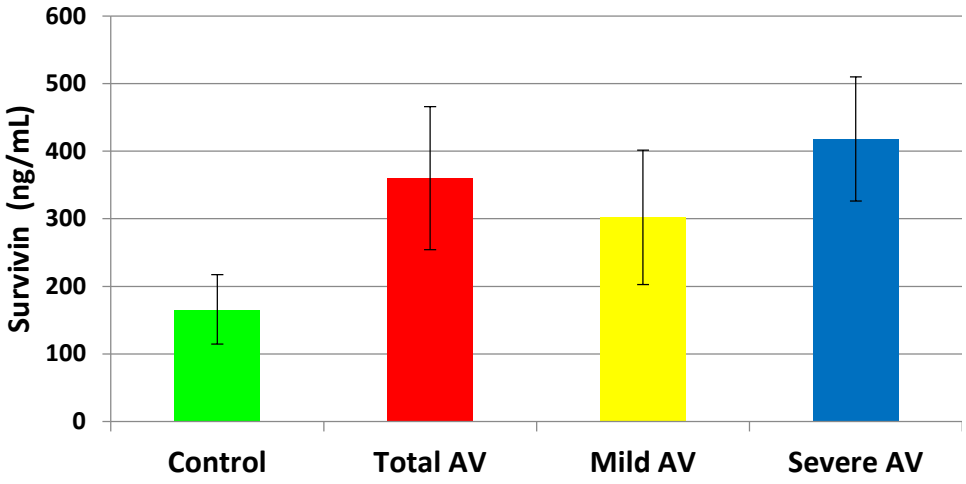

Figure (2). Bar chart for survivin concentration in all studied groups.

Table (4): Comparison of Survivin concentration between scar types in severe acne vulgaris group.

	Survivin concentration (ng/mL)			*P*
	N	**mean**	**± SD**	
Icepick	22	418.8	± 99.6	0.570[A]
Boxcar	5	444.1	±54.5	
Rolling	3	371.3	±83.7	

SD, standard deviation; A, ANOVA.

Discussion

Acne vulgaris is one of the commonest skin disorders which dermatologists have to treat, mainly affect adolescents, though it may present at any age. It is a chronic inflammatory disease of pilosebaceous unit [14]. Microcomedone is the earliest subclinical 'lesion' in acne that may change into open and closed comedones and into different inflammatory lesions, such as papules, pustules, nodules and cysts [2].

This case-controlled study was designed to evaluate serum level of survivin in different degrees of acne and it's relation to severity.

Our study showed that, AV (total and severe cases) had significantly higher frequency of excess sun exposure and stress when compared to control group. Severe AV cases had significantly higher frequency of excess sun exposure when compared to mild AV cases. This was in agreement with another

study which found that, 71% of their patients acne flared with stress [15].

Mean GAG score was 22.9. Severe cases had significantly higher frequency of back affection and higher GAG score when compared to mild cases. Scar was present in severe cases only. Other study [16] showed that, GAGS ranged from 8 to 37 and this was in the same range of the current study.

The present study observed that, most cases had icepick type (73.3%), 16.7% had boxcar type and 10% had rolling type. In agreement with, [5] who recorded that, icepick scar represented (60-70%), boxcar type (20-30%) and rolling type (15-25%).

AV (total, mild, severe) groups showed significantly higher survivin when compared to control group ($p<0.001$ for each). In addition, severe cases had higher survivin level when compared to mild cases ($p<0.001$). This was in agreement with previous study which found that the serum levels of survivin were markedly increased in the active acne and the acne scar groups in comparison to the healthy control group [11].

The increased serum levels of survivin and IGF-I in patients with acne vulgaris and post-inflammatory acne scar compared to controls draws attention to their possible role in the pathogenesis of them.

In addition, the study which revealed that, patients with severe degree of acne have higher levels of survivin than moderate. There were significant increased levels of survivin with increased severity of acne in patients with post-acne scar [17]. This could be explained by increased survivin levels leads to increased abnormal apoptosis that affects sebocyte survival, sebum production. Abnormal apoptosis and enhanced sebocyte survival mediated by survivin might affect infundibular keratinocyte differentiation and altered sebum production, leading to comedo formation and acne [18].

According to our results, all cases had gradual onset and progressive course. Face was affected in 100% of cases, back in 51.7%, chest in 26.7%. This was in agreement with the present study, which showed a high proportion of sebaceous glands (SG) found on the face (99%), back (60%) and chest (15%) [19]. Also, another study observed that the prevalence of facial acne was 89.1% and that of acne in the back 41.3% [20].

As regard to assessment of survivin level in diseases other than AV because studies exploring a relationship between serum

survivin and severity of acne are lacking ,Survivin-overexpressing cells were detected in the SSc dermis frequently, there was an increase of survivin expression in SSc fibroblasts, which might imply that TGF-β autocrine activation increased survivin gene expression at least partly through NF-κB activation, leading to apoptosis resistance through survivin anti-apoptotic pathways and TGF-β signaling So, increased SSc fibroblasts resistance to apoptosis has been associated with excessive fibrosis [13]. This may justify the role of survivin in formation of acne and acne scars.

Results of the present study revealed that, there were no significant differences in age and gender between total, mild, severe AV and control groups, also BMI did not differ significantly between all studied groups.

According to the present result, no significant differences were found in family history, smoking and fat diet between all studied groups.

No significant differences were found in Survivin concentration between scar types in severe acne vulgaris group.

Conclusions

From the results of present study, it is concluded that survivin is associated with the susceptibility of development of AV and has a role in its pathogenesis, severity and formation of acne scars.

Recommendations

The results of our study should be interpreted in light of its limitations, as the present study included a relatively small sample size. Further studies are needed to investigate the precise mechanisms by which survivin contribute to the pathogenesis of AV. We need more cases and using medicines that decrease fibrosis. Survivin is needed to be measured in tissue also and needed to be measured before and after isotretonin treatment.

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