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Serum survivin in acne versus post-acne scarring and the possible effect of isotretinoin therapy on its level

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Abstract

Introduction: Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit. Survivin is an apoptosis inhibitor protein, and it contributes crucially to cell cycle regulation. This study measures the serum level of survivin in acne and post-acne scarring patients, and assesses the possible effect of isotretinoin therapy on its level.
Methods: Sixty participants, including 40 acne patients (Group IA, IB), and 20 age- and sex-matched controls (Group II) were included. Group IA included 20 patients with active moderate-to-severe acne without scarring, and this group was further prescribed oral isotretinoin therapy for 3 months. Group IB included 20 patients with post-acne scarring of a duration not more than 6 months, without evident active acne lesions. Serum survivin levels were measured in the three groups using an enzyme-linked immunosorbent assay.
Results: There was a statistically significant higher serum survivin level in the acne scar group, followed by the active acne group, than in controls. In addition, there was a statistically significant reduction in survivin levels after treatment, and it was positively correlated with a reduction in the global acne grading system (GAGS) in the active acne group.
Conclusions: Survivin may play a role in the evolution of acne and acne scarring, and it could be a possible target for isotretinoin therapy.

Keywords: acne, scars, isotretinoin, therapy, survivin

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Introduction

Acne vulgaris is a common chronic inflammatory disorder of the pilosebaceous unit (1). It is a pleomorphic disorder, distinguished by microcomedones, pustules, papules, and nodules that all predominantly affect areas that are rich in sebaceous glands, such as the face, upper chest, and back (2–4). Its pathogenesis is complex and influenced by the interaction of four main factors: excess sebum production, disturbed follicular keratinization, colonization of the pilosebaceous duct by the anaerobic bacterium *Propionibacterium acnes* (renamed *Cutibacterium acnes*), and an inflammatory response (5–7).

Survivin, also called *baculoviral inhibitor of apoptosis repeat containing 5* (BIRC5), is a protein of the apoptosis inhibitor family, and it contributes to the control of cell division and chromosome separation. It is expressed while the cell cycle is in the G2/M phase (8). It has a length of 142 amino acids and is a 16.5 kD protein. It is encoded by the *BIRC5* gene located on the telomeric region of chromosome 17 (17q25), is expressed in both fetal tissue and tumor cells, and is inversely mediated by p53 (9–11). Nuclear survivin expression has been observed in sebaceous hyperplasia and neoplasia (12). Infundibular keratinocyte differentiation and sebum production may be impacted by abnormal apoptosis and increased sebocyte survival, both of which can be mediated by survivin, leading to acne development (4).

Oral isotretinoin therapy has been effective in controlling sebaceous activity in most cases of severe acne vulgaris. Isotretinoin induces sebocyte apoptosis through the activation of p53-mediated signaling. As a result, the pilosebaceous unit will have less survivin expressed and fewer anti-apoptotic effects, leading to sebocyte apoptosis (13–16).

Methods

Study design and population

This case-control prospective study was conducted on 60 participants recruited from the outpatient clinic of the Dermatology, Venerology, and Andrology Department at Alexandria Main University Hospital in Egypt. Informed written consent was obtained from all participants from December 2020 to June 2021 upon acquiring the approval of the Institutional Medical Ethics Committee (serial no. 0106526/2020, IRB no. 00012098). The participants were assigned to three groups: Group IA, Group IB, and Group II.

Group IA included 20 patients with active moderate-to-severe acne vulgaris without scarring, and this group was further prescribed oral isotretinoin therapy for 3 months. Group IB included 20 patients with post-acne scarring present for not more than 6 months, without evident active acne lesions. Group II included 20 age-, sex-, and body mass index (BMI)–matched control individuals.

Patients that had received any treatment for acne in the previous 3 months or received oral isotretinoin therapy in the previous 6 months were excluded. Patients with a history of previous skin resurfacing, acute or chronic hepatitis, benign or malignant tumors, liver cirrhosis, human immunodeficiency virus infection, obesity, or any other cutaneous or fibrotic disorders were excluded as well. Pregnancy, lactation, and hyperlipidemia were additionally excluded in patients that planned to receive oral isotretinoin therapy.

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Study protocol

All participants were subjected to the following:

1) Detailed history taking, including personal history, history of acne regarding the course, duration, medications received, history of other skin diseases, detailed menstrual history including age of menarche, menstrual cycle pattern, use of oral contraceptive pills in females, and family history of acne or acne scarring.
2) General dermatological examination to exclude any other dermatological condition, and calculation of BMI.
3) Local dermatological examination: a) evaluation of acne severity using the Global Acne Grading System (GAGS) in Group IA, whereby a score of 1 to 18 was considered mild, 19 to 30 moderate, 31 to 38 severe, and > 39 very severe (17); and b) evaluation of acne scarring according to type (ice pick, boxcar, rolling, or mixed) and its severity using Goodman and Baron's quantitative scar scale in Group IB (18).
4) Laboratory investigations: including routine investigations, such as CBC, liver and renal function tests, and lipid profile.
5) Isotretinoin treatment: Group IA was further subjected to oral isotretinoin treatment for a duration of 3 months at a dose of 0.5 to 1 mg/kg body weight per day.
6) Survivin level measurement: a) specimen collection: 3 ml of venous blood was collected by vein puncture under complete aseptic technique from every participant, then put in a sterile, dry, clean separator gel tube for serum isolation and left to clot at room temperature for 10 to 20 minutes. After clotting, centrifugation of the samples was performed (at 2,000 to 3,000 rpm) for 20 minutes, and then the supernatants were collected. The serum was separated and stored immediately at –20 °C until the measurement of survivin. Another venous blood sample was collected from the active acne group (Group IA) after receiving oral isotretinoin therapy for 3 months in the same manner; b) Measurement of serum survivin: survivin was measured in serum samples using the ELISA kit (Bioassay Technology Laboratory, Shanghai Korain Biotech Company (China) catalog number E1612Hu) (19).

Statistical analysis

With the aid of the IBM Statistical Package for the Social Sciences (IBM SPSS) software package version 20.0 (Armonk, NY: IBM Corp), the data were fed into a computer and evaluated. Numbers and percentages were used to describe qualitative data. The normality of the distribution was examined using the Shapiro–Wilk test. The range (minimum and maximum), mean, standard deviation, median, and interquartile range were used for quantitative data. The significance of the results obtained was evaluated at the 5% level.

Results

There was a female predominance in all groups (IA, IB, and II) with a female-to-male ratio of 3:1, 2.5:1, and 2.5:1, respectively. The age in Group IA ranged from 14 to 25 years with a mean of 19.50 ± 3.40 years, whereas that in Group IB ranged from 16 to 25 years with a mean of 19.75 ± 2.45 years, and in Group II it ranged between 15 and 24 years with a mean of 19.35 ± 2.46 years. There was no statistically significant difference between the three groups studied regarding age (p = 0.901) and sex (p = 0.921). There was no statistically significant difference in BMI between the groups studied (p = 0.759). The duration of the disease in the active acne group (IA) ranged from 4 months to 3 years, and in the acne scar group the duration ranged from 2 to 6 months. Forty-five percent of the participants with active acne had a positive family history of acne, whereas in the acne scar group only 20% of the cases had a positive family history of post-acne scarring.

According to the GAGS, active acne patients were divided into two groups: 11 cases (55%) with a moderate degree and nine cases (45%) with a severe degree. According to Goodman and Baron's Quantitative Scar Scale, Group IB patients were divided into three groups: mild (10 cases, 50%), moderate (eight cases, 40%), and severe (two cases, 10%). The icepick type of acne scars was represented in 50% of the cases, the rolling type in 15%, and the boxcar type in 10%. A mixed type of acne scar was represented in 25% of the cases studied.

After measuring serum survivin levels using ELISA, there was a statistically significant higher survivin level among the scar group compared to the active acne group (p = 0.008) and control group (p < 0.001). There was also a statistically significant higher survivin level in the active acne group compared to the control group (p < 0.001; Fig. 1).

The results of this study showed that there was a statistically significant positive correlation between serum survivin and dis-

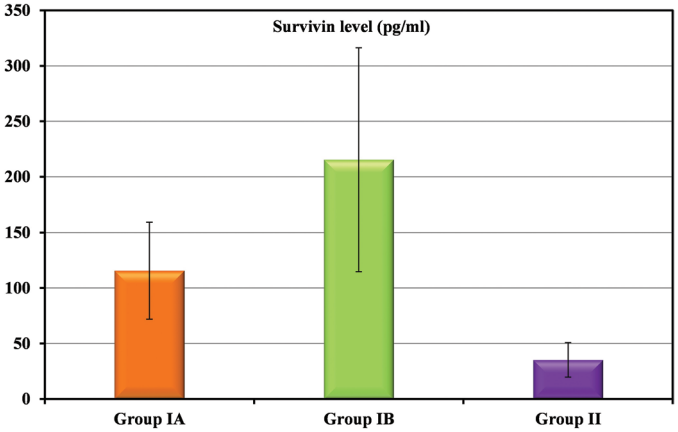

Figure 1 | Comparison between serum survivin levels in acne (IA), acne scarring (IB), and control (II) groups.

Table 1 | Relation between serum survivin level and disease severity in acne (IA) and acne scar (IB) groups.

Severity grade	Group IA (n =20) survivin level (pg/ml): Global Acne Grading System (GAGS)	Group IB (n = 20) survivin level (pg/ml): Goodman and Baron's quantitative scare scale
Mild (mean ± *SD*)	–	145.63 ± 70.97
Moderate (mean ± *SD*)	90.20 ± 5.10	272.25 ± 78.51
Severe (mean ± *SD*)	146.74 ± 50.30	337.76 ± 7.46
Significance between groups	$p \leq 0.001$*	$p = 0.005$*

SD = standard deviation.
*statistically significant at $p \leq 0.05$.

ease duration in Group IA and IB (r = 0.643, 0.518, p = 0.002, 0.019, respectively). There was also a statistically significant higher survivin level in the severe grades of both acne and acne scars in comparison to the lower grades (p < 0.001, p = 0.005, respectively; Table 1). On the other hand, there were no statistically significant correlations between survivin and both age and BMI in the case groups (Group IA and Group IB), but a statistically significant correlation with disease duration was detected in both groups (Table 2). Furthermore, Group IB showed a statistically significant increase in survivin levels among cases with the mixed scar type compared to those of the other types (p = 0.009; Table 3).

A statistically significant reduction in serum survivin level was detected in the active acne group after 3 months of isotretinoin therapy (p < 0.001; Table 4). There was a statistically significant positive correlation between the reduction of both survivin level and GAGS after treatment (r = 0.664, p = 0.001; Fig. 2).

Discussion

Acne vulgaris is a common inflammatory skin condition that affects the pilosebaceous units. Genetics, the androgen stimulation of sebaceous glands with abnormal keratinization, *Cutibacterium acnes* colonization, and pathological immune response to inflammation are the factors contributing to its pathogenesis (20). Survivin is one of the members of the apoptosis inhibitor family (21). It is a 16.5 kD protein that controls cell division and proliferation (4).

This study was conducted to evaluate the serum levels of survivin in acne and post-acne scarring and the response to isotretinoin therapy through the estimation of serum survivin levels in the groups studied and comparing them with those in healthy individuals using the ELISA test. The active acne group was subjected to oral isotretinoin therapy for 3 months, and the serum survivin level was measured before and after the defined period. There was a statistically significant difference in serum survivin level among the three groups studied, showing the highest levels in the scar group, followed by the active acne group and then the control group.

The studies by Assaf et al. (22), Mohammed et al. (23), Aksoy et al. (24), and El-Tahlawi et al. (4) agree with the present results in that a statistically significant increase in serum survivin levels is reported in the active acne and post-acne scar groups compared to the control groups. The first two studies show the highest levels among the acne scar groups, as in our study. However, the study by El-Tahlawi et al. (4) shows that the active acne patients have higher levels of survivin than the patients with acne scars.

This was explained in a previous study by Bowen et al. (25), who reported a rise in survivin in the inflammatory and proliferative phases of keratinocytes, which play a significant role in the development of acne lesions. Acne is distinguished by the excessive production of sebum with high amounts of monounsaturated, pro-inflammatory lipids, resulting from exaggerated sebocyte activity, which is induced by increased insulin, such as insulin-like growth factor 1 (IGF-1) and androgen signaling (26). Acne is associated with increased activity of the mechanistic target of rapamycin complex 1 (mTORC1) (27). Activated IGF-1/mTORC1 signaling promotes the expression of the anti-apoptotic protein survivin. Interestingly, serum IGF-1 levels of acne patients have been significantly correlated with survivin expression (13).

It is reported that enhanced survivin expression promotes fibroblast apoptosis resistance in idiopathic pulmonary fibrosis (28). This shows that the expression of survivin may be related to the pathophysiology of fibrosis in many disorders, including acne scarring, and thus the suppression of its expression could be a suitable alternative for reversing these lesions. This is explained by the fact that acne-related inflammation and immunological responses raise oxygen consumption, which causes localized tissue hypoxia. The up-regulation of survivin under hypoxic conditions is mediated by Notch-1 signaling, hypoxia-inducible factor 1α (HIF-1α), and transforming growth factor-β (TGF-β) (29, 30).

This study revealed a statistically significant higher serum survivin level in patients with higher grades of acne severity. Similarly, the studies by Mohammed et al. (23), Tahlawi et al. (4), and Aksoy et al. (24) reported the same finding.

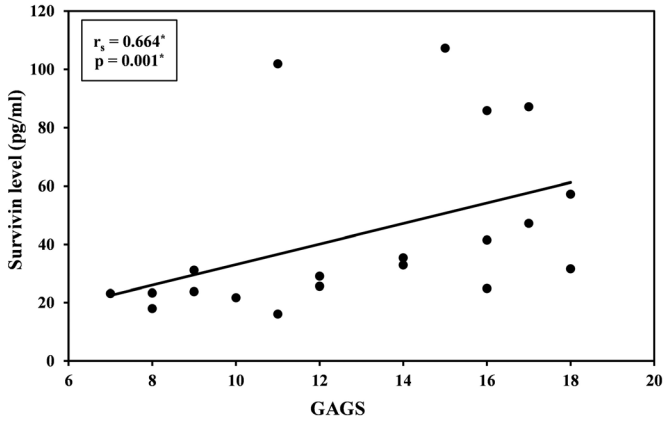

Figure 2 | Correlation between reduction in survivin level and Global Acne Grading System (GAGS) in Group IA (active acne) after isotretinoin therapy (n = 20).

Table 2 | Correlation between baseline survivin level and age, body mass index, and duration in active acne and acne scars groups.

Survivin level (pg/ml)	Active acne group (IA)		Acne scar group (IB)	
	r_s	p	r_s	p
Age (years)	−0.199	0.401	−0.071	0.765
BMI (kg/m²)	0.053	0.826	0.105	0.661
Disease duration (years)	0.643	0.002*	0.518	0.019*

BMI = body mass index, r_s = Spearman coefficient.
*statistically significant at $p \leq 0.05$.

Table 4 | Comparison between serum survivin levels before and after isotretinoin treatment in active acne group (IA).

Survivin level (pg/ml)	Before treatment	After 3 months of treatment	Z	p
Range	82.49–212.39	58.68–110.47	3.920*	< 0.001*
Mean ± SD	115.65 ± 43.72	72.38 ± 16.26		

SD = standard deviation, Z = Wilcoxon signed ranks test.
*statistically significant at $p \leq 0.05$.

Table 3 | Relation between survivin level and scar type in acne scar group (Group IB).

Acne scar type	n	Survivin level (pg/ml)			H	p
		Min.–Max.	Mean ± SD	Median		
Icepick	10	101.29–339.4	145.63 ± 70.97	120.62	11.653*	0.009*
Rolling	3	156.82–301.2	214.30 ± 76.56	184.87		
Boxcar	2	197.14–339.4	268.27 ± 100.6	268.27		
Mixed	5	322.59–343.03	334.82 ± 8.0	335.39		

SD = standard deviation, H = Kruskal–Wallis H test.
*statistically significant at $p \leq 0.05$.

When the serum survivin levels in the active acne group were compared by sex, no statistically significant difference was detected. This is in accordance with the studies by El-Tahlawi et al. (4), Assaf et al. (22), and Mohammed et al. (23). In contrast, the study by Aksoy et al. (24) showed statistically significant higher levels of survivin in females than in males among the active acne group.

Regarding the relation between survivin level and the clinical data of the acne scar group, there was a statistically significant elevation in survivin levels among patients with the mixed type of scars compared to those of the other types. On the other hand, the study conducted by Mohamed et al. (23) showed that the boxcar type has the highest serum level of survivin.

There was a statistically significant reduction in survivin levels in the active acne group after receiving the course of oral isotretinoin therapy. Isotretinoin-mediated sebocyte death is explained by binding to and activating retinoic acid receptors (RARs), and this impacts gene expression. As a result, the transcription factor p53 rises. Isotretinoin apparently reduces the amount of sebocyte progenitor cells and their survival via enhanced p53 signaling. Patients with acne have higher levels of IGF-1 expression in the basal and suprabasal layers of their sebaceous glands. More importantly, p53 has been identified as a negative regulator of the IGF1R gene. Therefore, the inhibition of IGF-1 signaling mediated by p53 decreases the expression of survivin and its anti-apoptotic effects in the pilosebaceous unit (12, 31, 32). Increased p53 has a negative impact on survivin levels, and this is the net result of isotretinoin treatment. Because isotretinoin stimulates p53 gene expression, it is considered the key conductor between activated and reduced signaling pathways, such as apoptosis and lipogenesis (33). Thus, isotretinoin therapy is an effective therapy for acne with a remarkable decrease in the serum level of the anti-apoptotic survivin.

To the best of our knowledge, no available published studies to date have assessed the effect of isotretinoin therapy on serum levels of survival. However, the sample size was relatively small.

In conclusion, the findings of this study support the idea that survivin may have a crucial role in the development of acne vulgaris, as well as a more significant role in the pathogenesis of post-acne scar formation. In addition, survivin could be a possible target for oral isotretinoin therapy.

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