

## Some Psychosocial and Biological Aspects in Vitiligo

Youssef El-Bayoumy, El-Sayed Saleh\*,  
Basem Salama El-Deek\*\*, and Mohamed Ali Attwa \*\*\*

### Abstract

**V**itiligo is a socially handicapping dermatologic disorder and its exact pathogenesis is not yet known. This study aimed at investigation for possible relationships between some clinical parameters (duration of illness, extent of body involvement) some hormonal changes as well as some psychosocial parameters (stressful life events, depression and anxiety) in patients with recent-onset vitiligo.

**Subjects and Methods:** A case-control design was utilized, in which, 30 vitiligo patients and 30 controls were assessed through: (1) general examination, (2) dermatological assessment (3) psychiatric and neuropsychological assessment: and (4) laboratory assessment: skin biopsy and measurement of cortisol, norepinephrine and  $\beta$ -endorphin levels in the blood.

**Results:** Most of the patients had segmental and focal vitiligo and the average duration was 12 days. Psychosocial parameters as well as blood levels of all the studied hormones were significantly higher in vitiligo patients than in the control group ( $P < 0.001$  all). In addition,

significant positive correlation was found between clinical parameters and psychosocial parameters as well as norepinephrin and  $\beta$ -endorphin blood levels ( $P < 0.01$ ).

**Conclusion:** Both  $\beta$ -endorphin and norepinephrin serum levels may reflect the psychosocial status of vitiligo patients. The duration and extent of vitiligo might be related to the patient's psychosocial status.  $\beta$ -endorphin and norepinephrin blood levels in vitiligo patients might be related to severity and aggressiveness of the disease. These results might support the theory that the psychosocial status may have a detrimental effect on the onset of vitiligo in predisposed persons.

### Introduction

Vitiligo is a socially handicapping dermatological disorder characterized by progressive depigmentation with unpredictable course which classically involves the integument and probably affects the pigmentary system of other organs (Hann and Nordlund<sup>(1)</sup>). The disease is believed to affect 1-4% of the general population (Le Poole et al<sup>(2)</sup>. and Ortonn and Bose<sup>(3)</sup>).

Departments of Dermatology & Andrology, \*Psychiatry,  
\*\*Community Medicine, \*\*\*Clinical Pathology. Faculty of  
Medicine Mansoura University

Although there has been extensive research into the cause of vitiligo, its exact etiology remains elusive (Lerner<sup>(4)</sup>; Puri et al<sup>(5)</sup>. and Mosher et al<sup>(6)</sup>). Several theories have been postulated concerning the possible cause of vitiligo, including: (i) Intrinsic (Genetic) theory; about 40% of cases have positive family history (Bhatia et al<sup>(7)</sup>; Majumder et al<sup>(8)</sup>, and Nath et al<sup>(9)</sup>). (ii) Self-destruction (autocytotoxic) hypothesis; failure of the normal protective antitoxic mechanisms (Mosher et al<sup>(6)</sup>; Hann and Chun<sup>(10)</sup>). (iii) Immune hypothesis; vitiligo is an autoimmune disease against melanocytes (Bystry<sup>(11)</sup>, Le Poole and Biossey<sup>(12)</sup>; Kovacs<sup>(13)</sup>). (iv) Neurogenic theory (neural pathogenesis); melanocytes are neural crest-derived cells (Reedy et al<sup>(14)</sup>). An increased release of catecholamines from the autonomic nerve endings in the microenvironment of melanocytes in the affected skin areas has been suggested (Lerner<sup>(4)</sup>; Durneva<sup>(15)</sup>; Schallreuter et al<sup>(16)</sup>; Al-Abadie et al<sup>(17)</sup>). (v) Biochemical theory (role of pteridines); In vitiligo there is increased production of tetrahydrobiopterins resulting in shortage of L-tyrosine (Adler et al<sup>(18)</sup>; Davis et al<sup>(19)</sup>; Schallreuter et al<sup>(16)</sup>).

Because the skin and psyche share embryonic origins, it is perhaps not surprising that psychological factors may affect the onset and progression of various skin conditions e.g. vitiligo (Papadopoulos et al<sup>(20)</sup>). The disease is usually preceded and accentuated by many psychosocial events e.g. disturbed self image, low self esteem and impaired quality of life. However, yet the exact etiology of vitiligo and its relation to psychological factors remain controversial.

The aim of this study was to investigate for the possible psychosocial factors related to development of vitiligo, and to find out possible correlations between these factors, duration and extent of the disease as well as blood levels of related stress hormones (cortisol, norepinephrin and  $\beta$ -endorphin). This might be a step toward clarification of the possible underlying etiology.

## Subjects and Methods

### Subjects:

Patients enrolled in this study were chosen

from the outpatient clinic of Dermatology, Mansoura University Hospital. The study involved 30 patients, (16 men, and 14 women) with definite newly-occurring vitiligo (one week to one month from onset).

In addition, 30 age and gender-matched healthy controls were recruited from the hospital personnel to participate in the study. Exclusion criteria for both cases and controls involved presence of any of the following conditions: other dermatological disorders, neurological disorders, major psychiatric disorders, such as life-time history of manic or depressive disorder, life-time history of psychotic symptoms or life-time history of unbearable severe stress or associated systemic illness e.g. thyroid disease or diabetes mellitus. All patients and control subjects were assessed with a comprehensive evaluation consisting of four sessions: dermatological, laboratory, psychiatric and psychological evaluations.

### Methods:

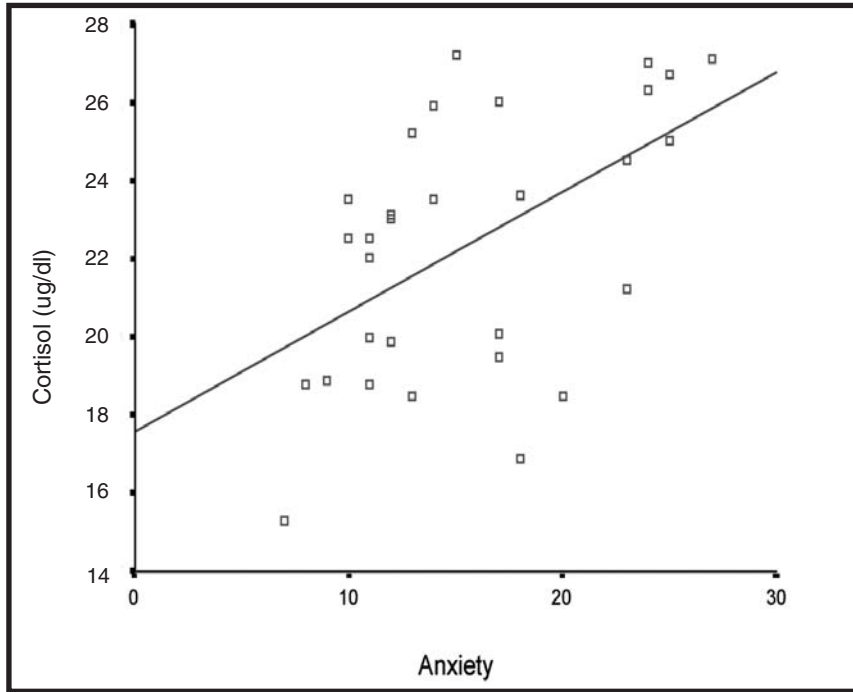
In this case control study, all patients and control subjects were subjected to the following:

**A- Thorough history taking and general medical examination;** stressing on age, gender, duration of illness, family history of the disease, associated diseases, .....etc.

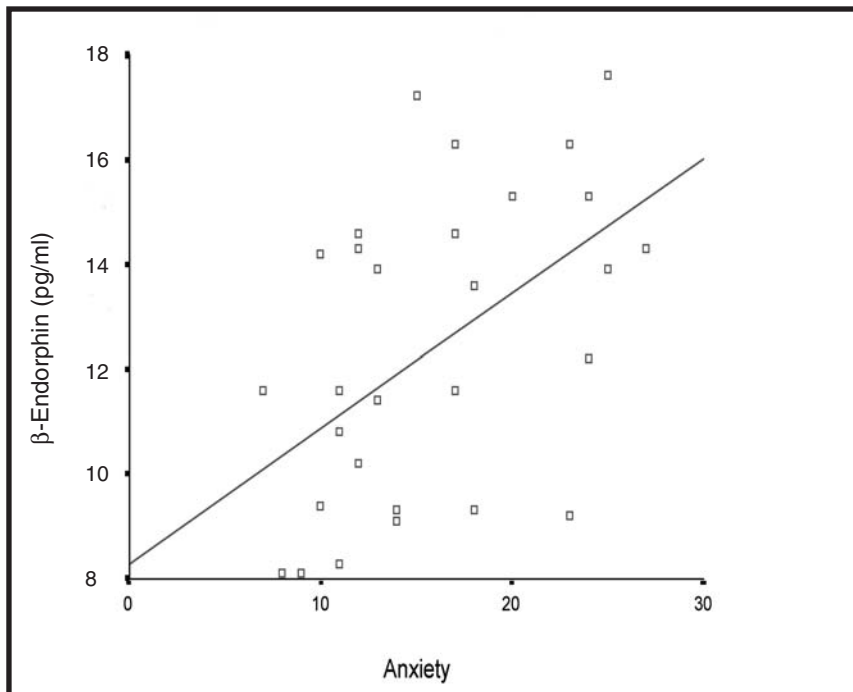
**B- Thorough dermatological assessment;** involving interview and dermatological examination. Cases have been classified according to the "categories" documented by Hann and Nordlund<sup>(1)</sup>; i.e. "localized" (focal, segmental, mucosal), "generalized" (acrofacial, vulgaris, mixed) or "universal". Cases have also been classified according to the "extent of body involvement with vitiligo" as documented by Naughton et al<sup>(21)</sup>, as follows: minimal vitiligo (less than 2% body surface), moderate vitiligo (2-5% body surface), extensive vitiligo (greater than 5% body surface).

**C- Psychiatric and Neuropsychological Assessment, involving:**

1. Clinical psychiatric examination focusing on detecting any existing psychiatric symptoms.
2. Applying Anxiety and Depression Inventory: it was developed by Shaheen and Rakhawy<sup>(22)</sup>.



**FIG .1.** Correlation between anxiety & cortisol.



**FIG .2.** Correlation between anxiety & beta-endorphin.

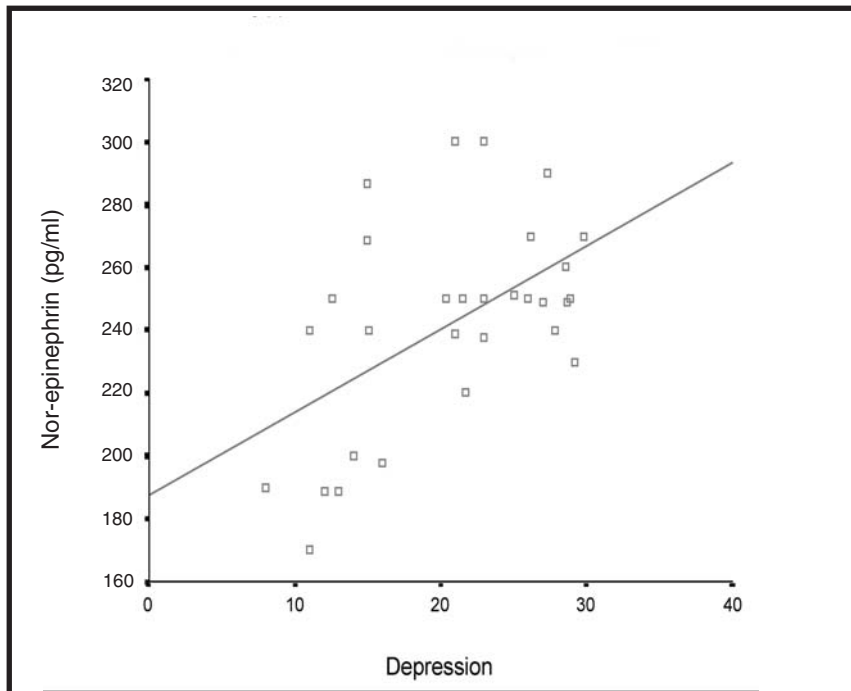


FIG .3. Correlation between nor-epinephrin & depression.

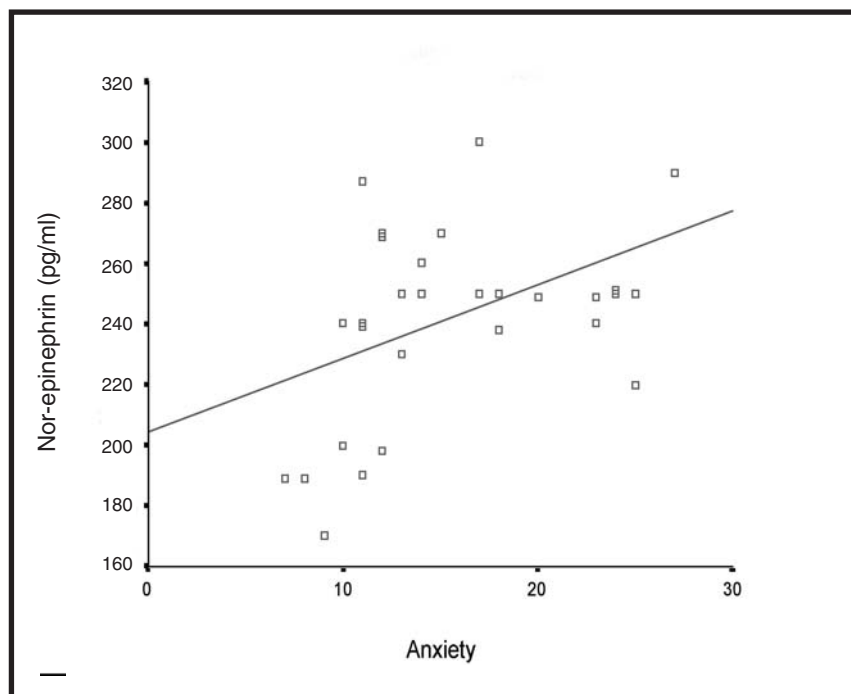
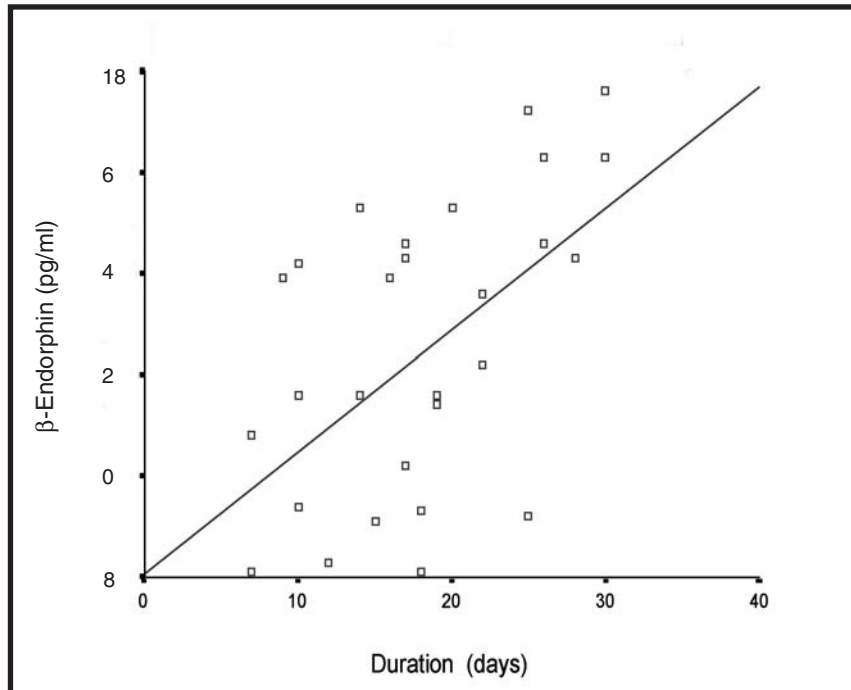


FIG .4. Correlation between nor-epinephrin & anxiety.



**FIG .5.** Correlation between  $\beta$ -endorphin & duration.

This personality test is constructed in an Egyptian slang language. It comprises 90 items, the first 30 items represent depression scale, the second 30 items represent anxiety scale and the third 30 items include social introversion scale. Scores of each scale can be classified according to presence or absence of psychiatric pathology into: (0-15) absent, (16-22) tendency and (22-30) present. To investigate the hypothesis of this study, we had stressed on anxiety and depression scales.

3. Life Event Questionnaire, it was developed by Horowitz et al<sup>(23)</sup> to assess the presumptive stress scores. Its scores can be classified into: no life crises (0-149), mild to moderate (150-299) and major life crises (> 300).

#### **D- Laboratory Assessment, involving:**

1. Skin biopsy stained by hematoxylin and eosin to confirm diagnosis.
2. Blood analysis for assessment of norepinephrine (pg/ml), cortisol (mg/dl) and  $\beta$ -endorphin (pg/ml) in blood. Samples for

“norepinephrine” and “ $\beta$ -endorphin” were collected in tubes containing EDTA and trasylol (5000 KIU/ 10ml). Plasma was separated immediately at 4°C and stored at -70°C until analysis which was made by radioenzymatic method (“Norepinephrine” ELISA, IBL- Immuno-biological Lab., Hamburg, Germany; “ $\beta$ -endorphin” Radioimmunoassay, Euro- diagnostica, AB, Malmo, Sweden). For “cortisol assessment”, serum was separated and stored at -20°C until analysis which was made by cortisol chemiluminescent method (DPC, Diagnostic Products Corporation, Los Angeles, CA, USA).

#### **Statistical analysis:**

Statistical analysis was done by using SPSS, statistical package for social science program version 10, 1999. “Kolmogorov – Smirnov” test was used to test for normal distribution. The data were parametric. The quantitative data were presented in the form of “number” and “percentage” and the “Chi-square” test was used for them. The quantitative data were presented as

“mean  $\pm$  standard deviation”. “Student’s t-test” was used to test difference between two groups, while, the “one-way ANOVA” test was used to test difference between three or more groups. “Pearson correlation coefficient” was used to study correlation between different variables.  $P \leq 0.05$  was considered to be statistically significant.

## Results

Age, gender and educational level of cases and control are shown in table (1). The age ranges from 12-73 years, mean  $38.7 \pm 18.7$  in cases versus 15-69 years, mean and  $38.4 \pm 18.1$ , in control. Male to female ratios were 16/14 and 14/16 in patients and control respectively. Most of patients (53.3%) and control (46.7%) were illiterate. Clinical features of vitiligo in studied patients are illustrated in table (2). Twenty percent of patients showed a positive family history. Regarding clinical types, generalised, acro-facial, segmental and focal, represent 20%, 13.3%, 33.3% and 33.3% respectively. Most of the cases (53.3%) had extensive vitiligo while both moderate and minimal vitiligo was found in 23.3% each. Duration of illness ranged from 7-30 days, mean  $12.9 \pm 3.5$ .

Prevalence of psychosocial parameters among patients is presented in table (3). Anxiety was found in 23.3%, depression was suffered by 48.3%, while 10% of cases faced major life crises. In Table (4), both psychosocial and hormonal parameters of patients versus control are demonstrated. All the studied psychosocial and hormonal parameters were higher in patients versus control ( $P < 0.001$  each).

Correlations between different studied parameters were shown in table (5) and figures 1, 2, 3, 4 & 5. Significant positive correlation had been found between “extent of vitiligo” and “life event scores” ( $r=0.58$ ,  $P < 0.001$ ), “depression scores” and anxiety scores ( $r= 0.48$  &  $0.49$  respectively,  $P < 0.01$  each). In addition, there had been also significant positive correlation between blood  $\beta$ -endorphin and each of life event scores, depression scores and anxiety scores ( $r=0.64$ ,  $0.62$  &  $0.58$  respectively,  $P < 0.001$  each). Similarly, serum norepinephrin showed significant positive correlation with life event scores ( $r= 0.72$ ,  $P < 0.001$ ) and each of depression

scores and anxiety scores ( $r= 0.52$  &  $0.43$ ,  $P < 0.01$  each). Moreover, significant positive correlation had been found between duration of vitiligo and blood levels of norepinephrine and  $\beta$ -endorphin ( $r= 0.54$  each,  $P < 0.01$  each). Also, there had been significant positive correlation between extent of vitiligo and the three hormones ( $P < 0.01$  each).

Table (6) shows comparison between different hormonal levels in patients facing different stressful life crises. Significant differences between blood levels of cortisol, norepinephrin and  $\beta$ -endorphin ( $P < 0.05$ ,  $P < 0.001$ ,  $P < 0.05$  respectively) had been found in patients with different levels of stressful life crises.

## Discussion

Because the skin and psyche share embryonic origins, various psychological factors, including emotional trauma and stressful live events, may affect both onset and progression of some skin conditions e.g vitiligo (Ortonne et al<sup>(24)</sup>. & Papadopoulous et al<sup>(20)</sup>). In this study, stressful life events questionnaire developed by Horowitz et al<sup>(23)</sup>, was utilized to assess the presumptive stress scores and this showed that our vitiligo patients faced stressful situations significantly more than their age, sex and educational level matched controls ( $t = 13.38$ ,  $p < 0.001$ ).

Prevalence of psychiatric morbidity in vitiligo was evaluated by Sharma and others<sup>(25)</sup> who found, depression and anxiety in 10% and 3.3% of their vitiligo patients respectively. After that, Mattoo and colleagues<sup>(26)</sup> found depression in 22%, and adjustment disorder in 56% of their vitiligo patients. In the present research, major life crises, anxiety and depression were found in 10%, 23.3% and 48.3% of vitiligo patients respectively. A highly significant difference was found between vitiligo patients and their matched controls regarding presence of depression and anxiety ( $t = 6.83$  and  $6.56$ , respectively,  $p < 0.001$  each). Moreover, significant positive correlation was found between psychosocial events, i.e. life events, depression and anxiety, and clinical features of vitiligo, i.e. extent of illness. Koshevenko<sup>(27)</sup> using photo-chemotherapy for treatment of vitiligo, found that, if combined with psychotropic drugs, and psychotherapeutic

sessions, this increased response to therapy by 20% and shortened the duration of treatment by half.

The vitiligo associated changes in the so called stress related hormones 'i.e. cortisol,  $\beta$ -endorphin and catecholamines' were investigated in other several studies and showed significant variations associated with both onset and progression of the disease. Stress can lead to an increased production of catecholamines which can induce depigmentation directly (Salzer & Shallreuter<sup>(28)</sup>, Goldstein et al<sup>(29)</sup>). Stress can also cause an increase in the production of adrenocorticotrophic hormone which in turn may cause increased production of corticosteroids (Hoes et al<sup>(30)</sup>). Emotional stress also has been suggested to precipitate vitiligo in some patients via increasing secretion of the opioid peptides,  $\beta$ -endorphin and met-enkephalin, which act as immunomodulators (Mozzanica et al<sup>(31)</sup>).

Most of these findings may be in accordance with those found in the present work. Extent of body involvement with vitiligo, referring to the disease severity, showed significant positive correlation with cortisol, norepinephrin and  $\beta$ -endorphin blood levels ( $r = 0.49, 0.50$  and  $0.49$ , respectively,  $P < 0.01$  each). In addition, statistically significant positive correlations had been found between blood level of norepinephrine and duration of vitiligo ( $r = 0.54$ ,  $p < 0.01$ ) and its extent (severity) ( $r = 0.50$ ,  $p < 0.01$ ).

The increased release of catecholamines from the autonomic nerve endings in the micro-environment of melanocytes in the affected skin areas has been suggested to be involved in the etiopathogenesis of vitiligo through the toxic effect of catecholamines and/or their o-diphenol metabolites against melanocytes i.e. "a cause rather than a result" (Morrane et al<sup>(32)</sup>, & Salzer and Shallreuter<sup>(28)</sup>). On the contrary, other researchers such as Orecchia et al<sup>(33)</sup>, and Cucchi et al<sup>(34)</sup>, suggested that the increase in catecholamine levels mainly occurring at the onset of the disease is probably due to stress associated with the appearance of lesions i.e. "a result rather than a cause".

Mozzanica et al<sup>(31)</sup>, and Caixia et al<sup>(35)</sup>, reported occurrence of increased secretion of the

neuropeptides  $\beta$ -endorphin and met-enkephalin leading to precipitation of vitiligo, and presence of positive correlation between the plasma met-enkephalin level and the aggressiveness of the disease. In addition, Caixia et al<sup>(35)</sup>, had found that the level of  $\beta$ -endorphin in vitiliginous lesions was significantly higher than in uninvolved skin. This background is strongly supported by results of the present study, where, the serum  $\beta$ -endorphin level was significantly higher in the patient group versus the control group ( $t = 10.55$ ,  $p < 0.001$ ) and significantly correlated with duration of vitiligo as well as its extent ( $r = 0.54$  &  $0.49$  respectively,  $p < 0.1$  each).

From the results of the present study, one can deduce that; (1) Both  $\beta$ -endorphin and norepinephrin blood levels may reflect the psychosocial status of vitiligo patients<sup>(2)</sup>. The duration and extent (severity) of vitiligo might be related to patient's psychosocial status namely, stressful life events, depression and anxiety. However, one could not exactly decide whether depression and anxiety are cause or result of vitiligo<sup>(3)</sup>.  $\beta$ -endorphin and norepinephrin blood levels in vitiligo patients might be related to extent (severity) of the disease.

Our results might support the theory that; the psychosocial status may have a detrimental effect on the onset of vitiligo in predisposed persons. However, on the other hand, one can not neglect the possibility of presence of some morbidity of vitiligo on the psychological state of the patients. All these data are to be taken into consideration on dealing with and counselling patients with vitiligo.

Further comprehensive studies involving people at risk for developing vitiligo, either through inheritance or through having other autoimmune disease, may be of value for prospective investigation of how life stresses affect the onset and course of vitiligo. In addition, further comprehensive studies monitoring stress related hormones e.g cortisol,  $\beta$ -epinephrine and catecholamines carried out over long periods, and recording the exact daily variations of these hormones may be of great value for investigation of the exact correlation between such hormones and various psychosocial factors as well as with various types of vitiligo separately.

**Table (1):** Some demographic features of patients and control.

	<b>Patient</b>		<b>Control</b>		
<b>Age</b>					
• Mean	38.7		38.4		
• SD	18.7		18.1		
• Range	(12-73)		(15-69)		P = 0.098*
<b>Gender</b>					
• Male / female	16/14		14/16		P = 0.26**
<b>Educational level</b>					
• Illiterate: No (%)	16	(53.3)	14	(46.7)	P = 1.46**
• Prepschool : No (%)	5	(16.7)	7	(23.3)	
• Secondary school: No (%)	2	(6.7)	4	(13.3)	
• College : No (%)	7	(23.3)	7	(16.7)	

\*: Student's t-test      \*\*: Chi: square

**Table (2):** Some clinical features of vitiligo in studied patients.

	<b>No</b>	<b>(%)</b>
<b>Family history:</b>		
• Positive	6	(20)
<b>Clinical type of vitiligo</b>		
• Generalised	6	(20)
• Acro-facial	4	(13.3)
• Segmental	10	(33.3)
• Focal	10	(33.3)
<b>Extent of body involvement:</b>		
• Minimal vitiligo (<2% surface)	7	(23.3)
• Moderate vitiligo (2-5% surface)	7	(23.3)
• Extensive vitiligo (> 5% surface)	16	(35.3)
<b>Duration of illness (in days):</b>		
• Mean ± SD	12.9 ± 3.5	
• Range	7 - 30	

**Table (3):** Prevalence of anxiety, depression and stressful life events among patients.

	No	(%)
<b>Anxiety</b>		
• Absent	17	(56.7)
• Tendency	6	(20)
• Present	7	(23.3)
<b>Depression</b>		
• Absent	9	(31)
• Tendency	6	(20.7)
• Present	14	(48.3)
<b>Stressful life event</b>		
• No life crises	2	(6.7)
• Moderate life crises	25	(83.3)
• Major life crises	3	(10)

**Table (4):** Psychosocial parameters and hormonal levels of patients versus control.

Parameter	Patient	Control	t
<b>Life event scale score</b>	207.67 ± 62.05	45.07 ± 19.32	13.38*
<b>Depression score</b>	20.73 ± 6.67	11.27 ± 2.24	6.83*
<b>Anxiety score</b>	15.7 ± 5.8	8.53 ± 1.28	6.65*
<b>Cortisol (µg/dl)</b>	22.37 ± 3.35	6.93 ± 1.71	20.68*
<b>Norepinephrin (Pg/ml)</b>	242.6 ± 33.27	160.2 ± 34.73	9.46*
<b>β-endorphin (Pg/ml)</b>	12.9 ± 2.9	6.39 ± 0.99	10.55*

\* P < 0.001

**Table (5):** Correlation between psychosocial parameters and each of the duration of disease, its extent and serum hormones.

Parameter	Life event Scale scores	Depression scores	Anxiety scores
	R P	R P	R P
Duration (days)	0.84 <0.001***	0.52 <0.01**	0.72 <0.001**
Extent of vitiligo (body surface area)	0.58 <0.001***	0.43 <0.01**	0.49 <0.01**
Cortisol (Pg/ml)	0.55 <0.01**	0.53 <0.01**	0.52 <0.01**
Norepinephrin (Pg/ml)	0.72 <0.001***	0.52 <0.01**	0.43 <0.01**
β-endorphin (Pg/ml)	0.64 <0.001***	0.62 <0.001***	0.58 <0.001***

“Pearson correlation coefficient”

**Table (6):** Comparison between hormonal levels between patients facing different stressful life event scores.

	No life crises	Moderate life crises	Major life crises	F#
<b>Cortisol (µg/dl)</b>				
• Mean	17.1	22.4	24.8	
• SD	2.54	2.97	4.07	3.94*
<b>Norepinephrin (pg/ml)</b>				
• Mean	179.5	242.3	286.6	
• SD	13.4	27.12	15.27	10.16***
<b>β-endorphin (pg/ml)</b>				
• Mean	9.8	12.9	15.9	
• SD	2.47	2.81	1.48	3.53*

# One way ANOVA test was used. \* p < 0.05, \*\*\*p < 0.001

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