

# Which stressors are responsible for the worsening in the clinical symptomatology of lupus?

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## ABSTRACT

**Objective:** The purpose of this study was to test which stressors worsen the symptoms perceived by patients with lupus, thus broadening and corroborating results obtained in a previous study published in *Psychosomatic Medicine*. **Methods:** In order to examine this question, we selected 43 patients with lupus whose symptoms worsened due to the effects of daily stress. These patients were divided into two groups: patients whose increase in clinical lupus symptomatology was predicted by an increase in daily stressors on the same day (G1) and patients whose increase in clinical lupus symptomatology was predicted by an increase in daily stressors the day before and the same day (G2). Later, three factorial analyses were conducted with the items related to stressors and the items related to lupic symptoms. **Results:** The results showed that in G1 there were three factors that made up a total of 35.08% of the explained variance. The stressors associated with certain symptoms of the illness in this group are feeling ill or being worried about their physical appearance, with the main stressor being the illness itself. However, in G2, two factors were found that made up a total of 40.37% of the explained variance for lag=0 and 38.67% for lag=1. The stressors associated with the majority of the lupus symptoms are of an interpersonal and work-related nature. This association was maintained when we carried out the factorial analyses with the items of the symptoms from the following day. **Conclusions:** The interpersonal and work-related stressors are related to a worsening in the majority of the lupic symptoms in the patients whose symptomatology worsens as a result of daily stress experienced the day before.

**Keywords:** Daily Stress; Interpersonal Stressor; Work-Related Stressors; Systemic Lupus Erythematosus

## 1. INTRODUCTION

Various studies have shown the devastating effect psychological stress has on certain rheumatic diseases [1]. Specifically, diverse studies have shown that stress is one of the environmental factors that can cause a worsening in lupus [2-8]. Although the role of stress in this illness appears clear, at first, there was certain controversy about the nature of the stressors, as some authors supported the theory that daily stress (not organizing time well, problems in social relationships...etc.) was mainly responsible for the worsening in lupus [2-4,6-8], while other authors defended a greater effect of the Extraordinary Stressful Life Events (death of a family member, car accident, etc.) on the lupus [5]. Although there is currently a lot of evidence that daily stress is primarily responsible for the worsening of this illness, few studies have shown which specific stressors are most related to this worsening. Specifically, three main studies were carried out with this objective. The first was conducted by Schubert *et al.* [4]. The authors studied a woman suffering from SLE during a 63-day period. In this patient, the concentration of neopterin (immunological parameter closely related to lupic activity in patients with SLE) in urine was measured daily, and her daily stressors were evaluated weekly. The findings showed that the moderately stressful incidents that led to a high level of emotional irritation and had stressful interpersonal implications increased the concentration of neopterin approximately one day later, that is, with a lag=1. Therefore, these stressors play a greater role in the increase in neopterin than other stressors. One problem of this study is that the sample studied is very small (only one SLE patient was evaluated), so that it is impossible to draw generalizable conclusions. Later, these authors performed a new study [6] where they evaluated daily (every 12 hours) the levels of stress, cortisol and neopterin in another lupus patient during a 56-day period.

They found that when the patient anticipated a moderate stressor (which in this case was the infidelity of her partner), her cortisol increased 24 hours before the incident and lessened 12 hours after it had occurred. However, if the patient did not anticipate the incident, her cortisol increased 24 hours after the incident and decreased 36 hours after it. With regard to the neopterin, these authors found that after exposure to the stressor there was a reduction in the amount of neopterin in the following 36 hours, producing a new increase in the next 60 hours. In this way, the authors again showed the modulation of the immune system due to stressful events involving interpersonal relationships, and due to the anticipation of these stressors, in the following 24-36 hours. The latest study carried out with the objective of defining the type of stressor that can affect the worsening of lupus is the one by Pawlak *et al.* [7]. These authors studied the stressors in 41 women with lupus during a six-month period and their physiological correlates (complement activity, anti-dsDNA and ECLAM-European Consensus Lupus Activity Measurement). The results showed that the patients who had a larger number of social obligations presented more outbreaks (92%) than the patients who had fewer social obligations (39%). Furthermore, these authors found an increase in the interpersonal relationship conflicts in the month prior to the lupic outbreak in the patients who experienced a worsening in the disease.

As we can see, all of these studies seem to clearly agree that the stressors most related to the worsening of the disease are not only of a daily nature, but they also have a clear component related to interpersonal relationships. However, in addition to the different stressors common to the general population, there have been no studies on the effects that the perception itself of the worsening of the disease (another stressor) has on this worsening. Likewise, no studies been carried out to test whether experiencing different stressors acts on some target organ of the disease, thus produces its worsening (joints, skin, etc.), or whether, on the contrary, it acts on a general level by activating all the systems.

Therefore, the purposes of the present study were, on one hand, to test what types of stressors are responsible for the worsening in the clinical symptomatology of lupus and, on the other, to find out what physical symptoms are involved in this worsening. These were tested in a group of patients that had already been evaluated and classified according to the effect that the stress had on their perception of the worsening of the disease [8].

## 2. PATIENTS AND METHODS

### 2.1. Study Population

64 patients originally participated in this study, of which 6 were later rejected because they had mixed connective tissue disease rather than lupus. Therefore, 58 lupus pa-

tients participated in the study, of which 50 were women and 8 men. 45 met at least 4 American College of Rheumatology (ACR) [9] criteria for classification as suffering from Systemic Lupus Erythematosus (SLE), and 12 were suffering from Chronic Lupus Discoid (CLD), diagnosed by their clinical history and an anatomopathological study. The mean age was 39.37 years (SD=9.72), and the mean educational level was 10.7 years (SD=3.44), which is equivalent to a bachelor's degree. The mean duration of the illness was 9.1 years (SD=6.38), the mean index of organ damage was 0.9 (SD=1.06), and the mean on the index of lupus activity was 1.73 (SD=3.2). All of the participants were patients at the Systemic Autoimmune Disease Unit at the University Hospital "Virgen de las Nieves" in Granada, Spain. They all had at least a minimum cultural background (they could at least read and write), and none of them presented any associated mental illness at the time of the study, although there were two patients with psychiatric histories. All of these patients gave their signed informed consent to participate in this study. Of these 58 patients, we only included the 43 patients for whom stress predicted a worsening in the clinical symptomatology of lupus. These subjects were classified into two groups: G1 with 31 patients whose increase in the clinical symptomatology of the lupus was predicted by an increase in daily stressors on the same day; and G2 with 12 patients whose increase in the clinical symptomatology was predicted by an increase in daily stressors the day before and the same day.

### 2.2. Information Collected

#### 2.2.1. Daily Stress Inventory (DSI)

The translation and adaptation to the Spanish population of the Brantley, Waggoner and Jones Daily Stress Inventory (DSI) was carried out by Peralta-Ramírez [10]. For this adaptation, they used the responses to a complete version of the DSI given by a broad sample. They then created a 20 item version comprised of some items that remain identical (e.g., "I forgot something"), others that are worded in a different way (e.g., "gave up an undesirable habit: eating too much, smoking, etc" for "gave up a habit that was not good for him"), and others that grouped various items from the DSI with related criteria ("Had problems in his relationship with other people: was criticized, ignored, interrupted when speaking..."). This instrument measures stressful daily events and the degree of stress produced by each of them in the last 24 hours. It contains 20 items that are categorized from 0 to 6, depending on the degree of stress they have caused, keeping in mind that 0 is no stress experienced and 6 means the event caused panic. The instrument's reliability coefficient is 0.82, the Cronbach alpha coefficient is 0.88, and its discriminated validity is 74.86% correct classification.

Therefore, the instrument presents high validity for detecting change [10]. The items related to this instrument are included in **Table 1**.

**Table 1.** Items from the DSI and the SLI.

ITEMS FROM THE DSI
I1. Had problems at work, with a specific activity
I2. Did not organize his or her time well
I3. Had problems in his or her relationships with other people (was criticized, ignored, and interrupted when speaking...)
I4. Has not slept soundly
I5. Forgot something
I6. Felt or feared being ill
I7. Had some small accident
I8. Thought about the future
I9. Played a sport or game poorly
I10. Did something he or she did not want to do
I11. Lost something or couldn't find something he or she was looking for
I12. Bad weather affected him or her
I13. Challenged someone in authority
I14. Heard bad news
I15. Something related to his or her personal appearance affected him or her
I16. Was faced with a feared situation or object
I17. Worried about other people's problems
I18. Barely escaped something dangerous
I19. Gave up a habit that was not good for him or her
I20. Had economic problems
ITEMS FROM THE SLI
S1. Loss of appetite
S2. Joint pain
S3. General malaise
S4. Fatigue
S5. Skin rash
S6. Abdominal symptoms
S7. Difficulty breathing

**2.2.2. SLE Symptoms Inventory (LSI)**

This inventory was elaborated by the group of medical specialists in the Systemic Autoimmune Disease Unit of the Internal Medicine Service at the University Hospital "Virgen de las Nieves" in Granada [11]. It refers to 8 symptoms suggestive of SLE activity, namely loss of appetite, joint pain, general malaise, fever, tiredness or fatigue,

skin rash, difficulty breathing and abdominal symptoms. These items are categorized from 1 to 10 according to the degree of intensity of these symptoms on that day. This inventory was designed to evaluate the subjective symptoms of large groups of SLE patients in clinical studies. We tested its internal consistency, as well as its concordance with physician reports and serological indicators

**Table 2.** Factors that relate certain items of stress with lupus symptoms on the same day in G1 and G2 (lag=0) and stress and symptoms the next day G2 (lag=1).

Ítems	G1 (lag 0)			Ítems	G2 (lag 0)		Ítems	G2 (lag 1)		
	Factor	Factor	Factor		Factor	Factor		Factor	Factor	Factor
	1	2	3		1	2		1	2	
S3	<b>0.829</b>	0.08	0.214	S1	<b>0.876</b>	-0.141	S4	<b>0.853</b>	0.159	
S4	<b>0.805</b>	0.05	0.253	S4	<b>0.843</b>	0.225	S7	<b>0.843</b>	0.224	
S2	<b>0.687</b>	0.02	0.242	S7	<b>0.837</b>	0.201	S3	<b>0.841</b>	0.156	
S1	<b>0.618</b>	-0.02	0.123	S3	<b>0.823</b>	0.228	S1	<b>0.838</b>	-0.024	
I6	<b>0.591</b>	0.131	-0.13	S2	<b>0.809</b>	0.259	S2	<b>0.270</b>	0.190	
I3	0.127	<b>0.711</b>	0.08	I1	<b>0.759</b>	0.170	I2	<b>0.691</b>	0.133	
I13	-0.07	<b>0.671</b>	0.03	I2	<b>0.756</b>	-0.003	I4	<b>0.646</b>	0.480	
S6	0.336	<b>0.505</b>	0.173	I4	<b>0.713</b>	0.354	I1	<b>0.629</b>	0.362	
I15	0.112	0.15	<b>0.807</b>	I6	<b>0.661</b>	0.267	S6	<b>0.588</b>	0.180	
S5	0.311	-0.02	<b>0.789</b>	S6	<b>0.555</b>	0.233	I6	<b>0.551</b>	0.413	
				I12	0.298	<b>0.695</b>	I12	0.235	<b>0.684</b>	
				S5	0.527	<b>0.662</b>	I8	0.416	<b>0.644</b>	
				I8	0.486	<b>0.606</b>	I17	0.193	<b>0.638</b>	
				I17	0.272	<b>0.532</b>	S5	0.514	<b>0.614</b>	
							I15	0.407	<b>0.559</b>	
Self-rating	5.973	2.102	1.396		9.313	1.588		8.861	1.581	
% Variance	22.123	7.785	5.175		34.493	5.881		32.819	5.858	

of disease activity. This instrument shows a high internal consistency of the LSI, with a Cronbach alpha of 0.862. Furthermore, a contingency analyses shows agreement between the medical report and the patient self-report on the same day for each of the lupus symptoms included in the LSI (difficulty breathing ( $p < 0.004$ ), joint pain ( $p < 0.001$ ), loss of appetite ( $p < 0.003$ ), general malaise ( $p < 0.005$ ), fatigue ( $p < 0.005$ ) and skin rash ( $p < 0.018$ )). This agreement is not found on the abdominal symptoms (LSI). On the other hand, we found differences between the LSI scores of the patients with high serological ac-

tivity and those of the patients with low serological activity ( $\chi^2(1) = 5.302$ ;  $p < 0.021$ ), with the former presenting higher scores than the latter. The LSI is a highly reliable and valid instrument for evaluating the subjective symptoms of the disease as well as their fluctuations. The items related to this instrument are included in **Table 1** too.

The SLE Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clin-ics/American College of Rheumatology (SLICC/ACR) Damage was evaluated in the prior study but the data were not included in this study [8].

**Table 3.** Summary of the relationship between the different stressors and lupus symptom.

G1		G2
Factors that relate certain items of stress with lupus symptoms on the same day and self-rating.	Factors that relate certain items of stress with lupus symptoms on the same day and self-rating.	Factors that relate certain items of stress with lupus symptoms the next day and self-rating.
<b>Factor 1:</b> 5.973	<b>Factor 1:</b> 9.313	<b>Factor 1:</b> 8.61
<b>*Felt or feared being ill</b>	<b>*Did not organize his/her time well</b>	<b>* Did not organize his/her time well</b>
General malaise	<b>*Has not slept soundly</b>	<b>* Has not slept soundly</b>
Fatigue	<b>*Had problems at work</b>	<b>* Had problems at work</b>
Joint pain	<b>*Felt or feared being ill</b>	<b>* Felt or feared being ill</b>
Loss of appetite	Loss of appetite	<b>* Felt or feared being ill</b>
<b>Factor 2:</b> 2.102	Fatigue	Fatigue
<b>*Had problems in his/her relationships with other people.</b>	Difficulty breathing	Difficulty breathing
<b>*Challenged someone in authority</b>	General malaise	General malaise
Abdominal symptoms	Joint pain	Loss of appetite
<b>Factor 3:</b> 1.396	Abdominal symptoms	Joint pain
<b>*Something related to his/her personal appearance affected him/her.</b>	<b>Factor 2:</b> 1.588	Abdominal symptoms
Skin rash	<b>*Bad weather affected him/her</b>	<b>Factor 2:</b> 1.581
	<b>*Thought about the future</b>	<b>* Bad weather affected him/her</b>
	<b>*Worried about other people's problems.</b>	<b>* Thought about the future</b>
	Skin rash	<b>* Worried about other people's problems</b>
		<b>* Something related to his/her personal appearance affected him/her..</b>
		Skin rash

### 2.3. Procedure

During the first week, the patients were recruited by the internist at the outpatient clinic for autoimmune diseases. At the routine check-up, the patient was given information about this study on the effects of stress and lupus and invited to participate (90% agreed). If the patient agreed, he or she was given an appointment for the first session. In the first session, the study was explained in detail, and subjects were asked to sign the consent form (99% accepted). The subjects who accepted underwent the following: 1) a clinical interview was carried out to find out basic data like age, educational level and diverse emotional problems occurring in his or her life; 2) the SLEDAI and SLICC/ACR were evaluated; 3) they were given 30 copies of the DSI and 30 copies of the LSI. Furthermore, every 15 days they were contacted by telephone in order to resolve any doubts about completing the questionnaires, and they were encouraged to continue to fill them out. They were informed that they would have to complete the DSI and LSI at the end of the day every day for six months (This was done by all

the patients, except three who left the evaluation early). Each month, they were provided with 31 IEC questionnaires and 31 LSI questionnaires, personally if they lived in Granada or by mail if they lived outside of Granada. Furthermore, every 15 days they were telephoned in order to resolve any doubts about completing the questionnaires, and they were encouraged to continue to fill them out.

### 2.4. Statistical Analyses

In a previous study published in the Journal Psychosomatic Medicine [8], 3 groups were used: G1: patients whose increase in the clinical symptomatology of the lupus was predicted by an increase in daily stressors on the same day (lag=0); G2: patients whose increase in the clinical symptomatology was predicted by an increase in daily stressors the day before and the same day (lag=0,1); G3: patients for whom daily stress did not predict any increase in the self-reported clinical symptomatology of the lupus. In the present study, data from two of the groups (G1, G2) were used for statistical analyses.

Secondly, with the objective of testing what types of



stressors are related to the worsening of the lupus symptomatology itself, the two established groups were used, and 3 factorial analyses were performed. Principal component analysis was used as a factor extraction method. To determine the number of factors to be extracted, a cut-off point was established of specific values superior to one. A factor rotation using the Varimax method was performed to strengthen the grouping of the variables around the associated factor. The registers noted in the rotated factors matrix represent the weights of the variables in relation to each factor, and they receive the name of factor charges. As this is an orthogonal rotation, its interval oscillates between -1 and 1. The first two factorial analyses were carried out with the scores on each of the items from the DSI and the scores on each of the items from the SLI for each of the groups, in other words, one factorial analysis per group (G1, G2). Later, based on results from the previous study [8], which showed that in some patients a worsening occurs in the clinical symptomatology of the lupus due to the effect of the stress from the previous day (G2), we moved the time series related to the items from the SLI questionnaire one square up with regard to the items on the DSI questionnaire, so that the items on one day of stress would be matched with the items on the lupus symptoms the next day (SLI). After this shift, a factorial analysis was performed using Varimax rotation with the scores on the items from the DSI and the scores on the items from the SLI; logically, this was only done for group G2.

### 3. RESULTS

#### 3.1. Factorial Analyses of Daily Stressors and Lupic Symptoms the Same Day

Two factorial analyses were performed, one for each group's "stressor-symptoms relationship" (see **Tables 2** and **3**). In the factorial analyses of G1, three factors were found that related stressors with symptomatology, and they explained 35.1% of the data variance. The main factor related four of the seven most common symptoms in lupus with the stressor "felt ill". The second factor seems to relate stressors that involve interpersonal relationships with stomach discomfort, and the third factor relates skin rashes with the stressor "his or her personal appearance affected him or her".

In the factorial analyses of G2, two factors were found that related stressors with symptomatology, and they explained 40.4% of the variability of the data. The main factor seems to relate 6 of the 7 lupic symptoms with stressors closely related to work-related stress and perception of the disease. In the second factor, stressors like worry about others' problems, thinking about the future and bad weather are related to skin rashes.

#### 3.2. Factorial Analyses Performed with the Daily Stressors and the Lupic Symptoms of the Next Day

The factorial analyses of G2 showed two factors that related daily stressors with lupic symptomatology, and they explained 38.7% of the variability of the data. Factor 1 related six of the seven lupic symptoms with stressors of a work-related nature and perception of a worsening of the disease. Furthermore, the second factor related skin rashes with stressors like "bad weather affected him or her", "he or she thought about the future", "he or she worried about others' problems" and "his or her personal appearance affected him or her" (see **Tables 2** and **3**).

### 4. DISCUSSIONS

After performing the factorial analyses between the items on the daily stress questionnaire and the items on the inventory of clinical symptoms of lupus, the classification established of the different effects of stress on the lupus symptoms (G1, G2) [8] is validated, as there is a consistent correlation between the different stressors and the lupic symptoms. Specifically, we can see how the patients' clinical symptomatology worsens on the same day, the majority of the lupic symptoms are related to the stressor "he or she felt ill", just as in another factor personal appearance (as a stressor) and skin rashes (as a symptom) were related. On the other hand, the results found with the patients whose symptomatology worsened the same day and the day after the stressful situation (G2) show that the same factors are found at two moments in time when the factorials were performed (stress and symptoms the same day, and stress and symptoms the next day). Here we found two factors. One factor relates six of the seven symptoms most characteristic of lupus with stressors of a work-related nature, such as "does not organize time well", "problems at work", etc., and health stressors like "feeling ill". The second factor relates stressors of a psychosocial nature, like worrying about others' problems or the future, etc., with the symptom of skin rashes.

As we can see, in the patients from G1, it seems more likely that the stressor "he or she felt ill" would be caused by the perceived symptoms than that this would be the causal agent of these symptoms. The same thing occurs with factor 3 for this group where the skin rashes are related to the stressor "his or her personal appearance bothered him or her". Finally, in the other factor we found different stressors are related to only one isolated item from the lupus symptom inventory (stomach discomfort), so that we can rule this out as being representative of the lupic symptoms. Instead, we would consider it more as a physical consequence of the stress in general.

The data found in G2 were very interesting, as they

show a clear relationship between the different work and health stressors and six of the seven symptoms associated with lupus. Likewise, the skin rashes are not related, as they were in the former group, with personal appearance, but rather with stressors regarding interpersonal relationships and worry about the future. It is noteworthy that in the group in which the worsening of the symptoms of the disease is predicted by the stress the day before, when we performed the factorial analyses with the stress data and the symptoms of the following day, the same factors remained and with similar self-ratings. These data do make it possible to state that certain stressors of a work and interpersonal nature produce worsening in the lupic symptomatology perceived the same day and the day after experiencing the stress.

The results found coincide, on one hand, with those obtained by other researchers [4,6,7], where the psychosocial stressors were related to the worsening in lupus activity. However, we were able to relate different types of stressors with certain specific symptoms of lupus, finding a great effect of the stressors related to work overload and to the perception of the illness itself. Furthermore, we went one step further in which we can define what types of stressors are related to a certain symptomatology. One piece of data which stands out is that skin rashes are not associated with other lupic symptoms in their relationship with the stressors. Instead, they are related to interpersonal relationship stressors.

In conclusion, this study highlights the importance of certain stressors in approaching stress in patients with lupus. Knowing which stressors are most related to the worsening of the symptoms provides us with guidelines for action and intervention in the diverse psychological therapies that are being conducted with the objective of providing lupus patients with psychological strategies for controlling stress and other related emotional variables [12-14]. Furthermore, the results obtained are an important tool for the medical specialist who works with these patients, as he or she can provide information of a preventative nature to patients, emphasizing the importance of avoiding work overload and controlling any possible interpersonal conflicts. Finally, the results found in this study corroborate the results found in the previous study published in Psychosomatic Medicine [8].

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