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Efficacy of Cognitive Behavioural Therapy for the Treatment of Chronic Stress in Patients with Lupus Erythematosus: A Randomized Controlled Trial

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Key Words
Lupus · Stress · Depression · Cognitive-behavioural therapy · Quality of life

Abstract
Background: Chronic stress worsens the quality of life (QOL) of lupus patients by affecting their physical and psychological status. The effectiveness of a cognitive-behavioural intervention in a group of patients with lupus and high levels of daily stress was investigated. ***Methods:*** Forty-five patients with lupus and high levels of daily stress were randomly assigned to a control group (CG) or a therapy group (TG); they received cognitive behavioural therapy (CBT) which consisted of ten consecutive weekly sessions. The following variables were evaluated at baseline and at 3, 9 and 15 months: (1) stress, anxiety, depression, (2) Systemic Lupus Erythematosus Disease Activity Index, somatic symptoms, number of flares, (3) anti-nDNA antibodies, complement fractions C3 and C4 and (4) QOL. A multivariate analysis of repeated measures and various analyses of variance were carried out. ***Results:*** We found a significant reduction in the level of depression, anxiety and daily stress in the TG compared to the CG and a significant improvement in QOL and somatic symptoms in the TG throughout the entire follow-up period. We did not find any significant changes in the immunological parameters. ***Conclusions:*** CBT is effective in dealing with patients suffering from lupus and high levels of daily stress as it significantly reduces the incidence of psychological disorders associated with lupus and improves and maintains patients' QOL, despite there being no significant reduction in the disease activity index.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin that can produce a broad spectrum of clinical symptoms (general malaise, fever, fatigue, weight loss, skin rashes or joint inflammation, anaemia, inflammation of the lymph glands, a reduced immune response and cardiac, kidney, neurological and pulmonary complications) and diverse immunological disorders. SLE is a syndrome that manifests itself to a greater or lesser degree depending on the convergence of an immune regulation disorder and a strong genetic component, as well as the influence of hormones

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and various external agents. In chronic cutaneous lupus (CCL), only the skin is affected. There are well-known factors that can produce flares of SLE and CCL, such as ultraviolet radiation, infections and unsupervised changes in treatment with corticosteroids or immunosuppressants. In addition, stress has been described as a trigger and may worsen the patient's condition in cases of SLE [1–10] and other autoimmune diseases [11, 12]. Some studies [3–10] have shown that chronic stress (low-intensity events repeated over time) is most strongly linked to deterioration in patients with the disease. Peralta-Ramírez et al. [8] evaluated 58 patients with lupus (46 with SLE and 12 with CCL) for 6 months and found that chronic stress worsened the symptoms of the disease to the greatest degree, and this was observed in up to 74% of patients. They also found that 21% of patients with higher levels of the disease experienced deterioration 1 day after stress was increased.

Recent studies have shown the efficacy of psychological therapies in different medical illnesses [13–16]. Some investigations have been carried out which focus on the psychological aspect of lupus, with the aim of reducing the disease's interference in the daily life of patients [17], improving social support and patients' levels of self-management [18–20] and developing coping skills in patients [21]. However, while considerable research has been carried out on interventions to counter stress in relation to other autoimmune diseases [22–24], there is only one study on the effects of reducing stress in lupus patients using cognitive behavioural therapy (CBT) [25]. In that study, the authors evaluated the effects of a biofeedback-assisted CBT (BF/CBT) for coping with stress that affects physical functions, pain and psychological adaptation in patients with SLE. Thus, they studied 92 patients with SLE and pain, and found that those undergoing BF/CBT experienced a greater reduction in pain and psychological dysfunction compared with the groups of patients who received the usual care or symptom monitoring support. The positive effects of BF/CBT on psychological functioning compared with the usual care were evident at a 9-month follow-up evaluation. No significant differences between the groups were found in terms of disease activity levels according to the SLE Disease Activity Index (SLEDAI) and Systemic Lupus Activity Measure-Revised.

Anxiety and depression, which are frequently caused by daily stress, are the most prevalent psychological disorders experienced by lupus patients, affecting up to 40% of patients in some series [26–28]. Furthermore, it is evident that lupus patients are dissatisfied with the treatment of both these disorders [29], indicating that lupus is currently being mismanaged and that patients' concerns are not being dealt with adequately. These disorders, together with the chronic nature of the disease and its implications, not only affect the patient's physical and psychological well-being, but they also seriously limit their quality of life (QOL). It is widely accepted that adequate coping strategies can improve the QOL of patients with lupus [30, 31].

For all of these reasons, we carried out a randomized controlled study with the main objective of verifying the efficacy of CBT for coping with chronic stress in patients with lupus by assessing the activity level of the disease, reported symptoms, psychological variables (stress, depression and anxiety), immunological parameters [antinative DNA (nDNA), complement fractions C3 and C4] and QOL.

Patients and Methods

This randomized controlled trial was approved by the relevant ethics and research committees and was registered.

Patients

This prospective study lasted 15 months and included patients with SLE and CCL who were treated in the Systemic Disease Unit. The inclusion criteria were: (1) patients with SLE with at least 4 American College of Rheumatology criteria or patients with a diagnosis of CCL made with a biopsy; (2) age 18 years and over, and (3) high levels of chronic stress (defined in our population as equal to or greater than 24 points for men and 27 for women on the Cohen Perceived Stress Scale) [28, 29]. The exclusion criteria were: (1) less than a year of follow-up in the Unit; (2) illiteracy; (3) not being available to attend the therapy sessions or follow the established recommendations, and (4) receiving treatment for an acute psychiatric condition.

Information about the date of diagnosis, activity level of the disease and number of flares in the year prior to the therapy was obtained from the patient histories.

Study Design

We invited all 200 lupus patients in the Unit to participate in the study; 70 of them agreed to take part and attend a meeting, during which they were informed about the relationship between lupus and stress, as well as the objectives of our study. They were provided with an information sheet and an informed consent document. Each patient was interviewed and filled out the Perceived Stress Questionnaire [32, 33] in order to establish their level of daily stress. The selected subjects with a high level of stress were randomly divided into 2 groups, i.e. the therapy group (TG) and control group (CG). Patients assigned to the CG received only standard medical care, consisting of the usual recommendations such as moderate exercise, a balanced diet and plenty of rest. Disease activity, psychological parameters and QOL were established at baseline (T_0) and then 3 (T_3), 9 (T_9) and 15 (T_{15}) months after

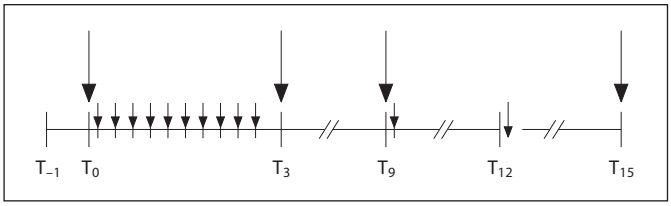

Fig. 1. Large arrows: measures of the psychological, analytical, immunological, disease activity and quality of life parameters at T_0 (basal) and after therapy: T_3 (3 months), T_9 (9 months), T_{15} (15 months). Small arrows: therapy sessions between T_0 and T_3; booster sessions after T_9 and T_{12}. T_{-1}: screening.

therapy was begun. The patients assigned to the TG attended 10 consecutive weekly CBT sessions lasting 2 h each between T_0 and T_3 (fig. 1), with 3 experienced psychologists. After T_9 and at 12 months (T_{12}), booster sessions were held with the objective of reinforcing the skills acquired.

Stress Management Program

A treatment manual was developed prior to the study [34]. The intervention consisted of 10 weekly group meetings lasting 1.5 or 2 h. Groups were made up of 7–9 patients. Each group session followed a structured format and consisted of the following elements: introduction to the session, discussion of homework, group discussion and the development of new coping skills. The sessions dealt with the following: (1) concept of stress; (2) cognitive restructuring – main errors in thinking; (3) cognitive restructuring – main central beliefs; (4) cognitive restructuring – challenging thoughts; (5) alternative thought control strategies – self-instructional training and thought stopping; (6) relaxation techniques – diaphragm breathing and deep muscle relaxation (the short circuits); (7) an approach to controlling pain oneself; (8) training in social skills – assertiveness techniques and basic assertive rights; (9) training in social skills – how to say no without feeling bad, asking another person to change their behaviour, and (10) humour and optimism as coping strategies. The groups were led by 2 clinical psychologists and a physician.

Psychological Parameters

To measure psychological parameters, we used the instruments listed below, which have all been validated in Spanish. The Stress Vulnerability Inventory [35, 36] assesses how vulnerable the subject is to the effects of stress. The Survey of Recent Life Experiences [37] gives an indication of the number of daily stressful events and the degree of stress produced by each of them in the past month, using a scale with a range from 1 ('has not been part of my life at all') to 4 ('has very much been part of my life'). The Beck Depression Inventory [38] is a self-administered questionnaire consisting of 21 items that assess the cognitive components of depression rather than the behavioural and somatic ones. This is not a diagnostic instrument, but it does give an indication of the depth of depression in patients with any diagnosis. The scores on this instrument can be classified into the following categories: no depression [10], slight depression [18], moderate depression [25] and severe depression [30]. Spielberger's State-Trait Anxiety Inventory (STAI) [39], created by Spielberg, Gorsuch and Lushene, contains 2 separate self-evaluation scales that measure 2 independent concepts of anxiety, i.e. state and trait. We evaluated trait anxiety (STAI-T).

Quality of Life

To measure QOL, we used the questionnaire SF-36 [40], which is a self-administered instrument with 36 questions that are divided over 8 subscales: physical function (the ability to carry out physical activities); physical role (measure of the interference of physical health in work or other daily activities); physical pain; general health (a health assessment carried out by the subject); vitality (the feeling of enthusiasm and energy the patient presents); social function (the ability to carry out normal social activities without interference from physical or emotional problems); emotional role (the interference of emotional problems at work and in other daily activities), and mental health (the feeling of peace, happiness and calm expressed by the patient). Furthermore, the SF-36 questionnaire makes it possible to calculate 2 psychometric measures, i.e. the patient's general level of physical health and the general level of mental health.

Disease Variables

The SLEDAI [41] was used to assess lupus activity. It consists of 24 items with preassigned values. The total SLEDAI score can range from 0 (no activity) to 105 (maximum activity). The SLEDAI has been shown to be sensitive to changes in lupus activity. This is measured by the treating physician, and the presence of symptoms is assessed according to a revised scale of somatic symptoms [42] which classifies them into 8 subscales (musculoskeletal, cutaneous, cardiovascular, respiratory, immunological, neurological, gastrointestinal and genitourinary).

All blood samples were routinely processed on the day of extraction using the standard techniques carried out by the clinical laboratory services in the hospital. They included a full blood cell count, erythrocyte sedimentation rate (Westergren method) C-reactive protein (immunoturbidimetric method), glucose, liver and kidney function tests, lipid profile, coagulation tests, complement fractions C3 and C4 (nephelometry), antinuclear antibodies (immunofluorescence), anti-nDNA (ELISA) and routine biochemistry. A decrease in the complement levels or an increase in anti-nDNA are indicators of a greater level of activity of the disease. Normal levels of C3 lie between 90 and 180 mg/dl and normal levels of C4 are between 10 and 40 mg/dl.

All variables were measured at T_0, T_3, T_9 and T_{15}. In cases of both SLE and CCL, the incidence of clinical flares in the year following the therapy (from T_3 to T_{15}) was compared with the incidence in the year before the study was carried out. An SLE flare was defined as a worsening of the disease, and in the case of CCL, a flare was defined as worsening of the existing skin lesions or the appearance of new lesions, which were always verified by a doctor from the unit.

Statistical Analysis

A multivariate analysis of repeated measures was used to analyse repeated measures in multiple time periods in the 2 groups, based on the general linear model, with Greenhouse-Geisser correction applied. This analysis identified whether the therapy had an effect on any of the variables (vulnerability to stress, perception of stress, depression, anxiety, somatic symptoms, SLEDAI,

Table 1. Characteristics of the patients with lupus (SLE and CCL) and high levels of daily stress at the beginning of the study

	TG (n = 21)	CG (n = 24)	p
Age, years	43.77 ± 9.88	40.41 ± 10.67	NS
Women, %	81.8	95.8	NS
SLE, %	80	79	NS
Patients undergoing treatment with corticosteroids, %	48	46	NS
Cumulated dose of corticosteroids, g	42.84 ± 26.54	39.34 ± 25.73	NS
Patients undergoing treatment with immunosuppressants, %	29	33	NS
Patients undergoing treatment with antidepressants, %	5	4	NS
Patients undergoing treatment with anxiolytics, %	19	16	NS
Level of education, years	9.5 ± 2.70	9.64 ± 2.59	NS
SLEDAI score	3.58 ± 3.75	3.93 ± 2.93	NS
Incidence of flares in the previous year	0.73 ± 1.09	0.35 ± 0.48	NS
C3, mg/dl	96.9 ± 20.3	96.2 ± 23.5	NS
C4, mg/dl	18.5 ± 12.5	18.1 ± 5.5	NS
Anti-nDNA, IU/ml	33.4 ± 65.22	17.8 ± 29	NS
Stress Vulnerability Inventory [35, 36]	12.6 ± 4.8	12.5 ± 5	NS
Survey of Recent Life Experiences [37]	89.8 ± 21	90.7 ± 19.3	NS
Symptoms reported	119 ± 42	129 ± 45	NS
Depression (Beck Depression Inventory)	14.6 ± 10	16.6 ± 11.3	NS
Anxiety (Spielberger's STAI)	64.5 ± 28.6	68.5 ± 24.8	NS
QOL (SF-36)			
PCS	39.28 ± 9.62	40.72 ± 11.8	NS
MCS	39.17 ± 12.8	38.28 ± 15.6	NS

PCS = SF-36 physical component summary; MCS = SF-36 mental component summary; NS = not significant.

number of flares, QOL) that was not experienced by the group that received normal care. Later on, in order to verify whether there were any differences between the 2 groups during each of the time periods, ANOVA was applied to the variables that were significantly affected, with the independent variable being the group (2 levels, i.e. CG and TG), and the dependent variable being each of the psychological, clinical and QOL measures. For the analysis of the within-group measures (values at T_3, T_9 and T_{15} compared to baseline), post hoc multiple-comparison analyses were carried out on the subjects from each of the 2 groups, the Bonferroni correction was applied and the p value obtained was 0.008. All the data were distributed normally. p values were two tailed. Calculations were carried out using the Statistical Package for Social Sciences, version 13.

Results

Description of Patient Characteristics

Duration of the disease, age at onset and level of education were similar among those who participated in the study and among the rest of the patients with lupus from the unit. Of the 70 patients who agreed to participate in the study, 20 did not present high levels of stress and 2 met some of the exclusion criteria (illiteracy and being physically unable to attend the sessions). The 48 patients finally selected [43 women (89%); 39 SLE patients (81%)] were randomly distributed to form the TG (n = 24) and the CG (n = 24). Three people who belonged to the TG dropped out during the course of the study; 1 patient dropped out due to pregnancy and because she was no longer willing to participate in the study, another patient dropped out because he/she was suffering from another serious disease at the same time and another because of a permanently elevated level of anti-nDNA, which produced unrelated variations in the results (outlier). The final number of study participants was 45. Both groups were similar in terms of age, proportion of women and men and proportion of SLE and CCL. Likewise, there were also similarities with regard to psychological aspects, incidence of flares of the disease and baseline SLEDAI (table 1).

Table 2. Analysis and effect sizes of the psychological variables and QOL

Measure	Group	T_0	p	T_3	p	T_9	p	T_{15}	p	Effect sizes		
										T_0–T_3	T_0–T_9	T_0–T_{15}
Vulnerability to stress (SVI)	TG	12.5 ± 4.9	0.963	7.8 ± 4[b]	0.017	7.5 ± 6.6[b]	0.050	6.3 ± 6.3[b]	0.001[a]	1.07	0.86	1.09
	CG	12.5 ± 5.9		11.6 ± 6		11.3 ± 6.1		12.1 ± 5.5		0.13	0.19	0.06
Perception of stress (SRLE)	TG	90 ± 21.6	0.776	79.2 ± 6.7	0.012	79.5 ± 16.7	0.011	82.3 ± 16.4	0.016	0.57	0.55	0.41
	CG	91.9 ± 19.8		93 ± 17.7		94.4 ± 20.1		99.2 ± 26.3		0.05	0.12	0.31
Depression (BDI)	TG	13.3 ± 10	0.308	7.8 ± 6.6	0.006[a]	10.3 ± 9.4	0.161	7.6 ± 7.2	0.003[a]	0.66	0.31	0.66
	CG	16.6 ± 11.2		17.1 ± 13.1		14.8 ± 11		16.5 ± 10.8		0.03	0.16	0.00
Anxiety (STAI-T)	TG	63 ± 28.2	0.465	44 ± 31	0.008[a]	43.4 ± 33.6	0.064	42.4 ± 26.4	0.007[a]	0.63	0.63	0.75
	CG	68.8 ± 24		69.1 ± 26.3		62.2 ± 30.4		66.5 ± 27.3		0.01	0.24	0.09
QOL (SF-36)												
Physical role	TG	57.1 ± 42.5	0.948	63.1 ± 39.2	0.118	65.4 ± 47.7	0.040	72.6 ± 40.2	0.005[a]	0.15	0.20	0.40
	CG	56.2 ± 45		42.4 ± 46.1		35.8 ± 45.1		34.7 ± 44.4		0.30	0.45	0.47
Pain	TG	42.1 ± 26.2	0.605	54 ± 22.6	0.123	52.2 ± 23.2	0.155	54 ± 22.7	0.123	0.48	0.41	0.49
	CG	46.7 ± 27.8		42.5 ± 25.6		41.9 ± 23.5		42.5 ± 25.6		0.15	0.18	0.15
Social function	TG	63.7 ± 26.8	0.838	79.7 ± 24.5	0.026	75.6 ± 25.7	0.099	79.7 ± 24.5	0.026	0.62	0.45	0.62
	CG	61.9 ± 30.2		60.8 ± 29.2		61.4 ± 29.6		60.8 ± 29.2		0.03	0.00	0.03
Mental health	TG	53.3 ± 19.1	0.594	67.4 ± 23	0.034	65.3 ± 23[b]	0.133	67.4 ± 23[b]	0.034	0.67	0.57	0.67
	CG	49.3 ± 26.1		51.1 ± 25.6		54.3 ± 24		51.1 ± 25.7		0.06	0.20	0.06
General health	TG	40.7 ± 19	0.461	52.5 ± 24.2	0.025	53.4 ± 22.5[b]	0.014	52.5 ± 24.2[b]	0.025	0.55	0.58	0.55
	CG	38.9 ± 22.4		29 ± 31.5		37.3 ± 21.9		37.3 ± 20.4		0.00	0.03	0.00

There were 21 patients in the TG and 24 in the CG. SVI = Stress Vulnerability Inventory; SRLE = Survey of Recent Life Experiences; BDI = Beck Depression Inventory.

[a] $p < 0.008$ in the between-group analysis; [b] $p < 0.008$ in the within-group analysis. Values of effect sizes greater than 0.5 signify at least a moderate effect of the therapy on the reported variable.

Effects of Stress Management on the Psychological, Clinical and QOL Variables

The averages, standard deviations, effect sizes and p values obtained from the analysis are shown in table 2. The effect size estimated for each of the variables analysed is shown in table 2. Values of effect sizes equal to or greater than 0.5 indicate a clinically significant improvement.

Psychological Variables

Stress. Repeated-measures ANOVA revealed significant changes in the TG in terms of the perception of stress ($F_{3, 40} = 3.001$; $p < 0.042$) and vulnerability to stress ($F_{3, 38} = 12.8$; $p < 0.000$). The between-group analysis showed significant changes in both variables in the TG at T_3, T_9 and T_{15} compared to the CG. The within-group analysis indicated that the TG experienced a significant improvement in both variables at T_3, T_9 and T_{15} compared to baseline. No differences were found in the CG.

Depression and Anxiety. The TG made better progress than the CG with regard to both variables throughout the follow-up as indicated by repeated-measures ANOVA [$F_{3, 38} = 6.285$, $p < 0.001$ for anxiety (STAI-T); $F_{3, 38} = 5.63$, $p < 0.002$ for depression]. A later analysis showed significant changes in depression and STAI-T in the TG patients when compared to the CG patients at T_3 and also in the longer term, at T_{15}. The within-group analysis showed that the TG patients presented lower levels of depression at T_3 and at T_{15} compared to their initial values and lower levels of anxiety at all 3 time points after the therapy. In the CG, no differences were found.

Clinical Variables

SLEDAI and Somatic Symptoms Scale Questionnaire. The results of these measures are summarized in table 3. With regard to the SLEDAI, the analysis of repeated measures did not produce significant results ($F_{3, 30} = 1.146$; $p < 0.330$), indicating that the changes observed in the TG were not different from those found in the CG. However, it did show a decrease in the mean SLEDAI score of the TG at T_3, with a trend toward significance ($p < 0.085$). The analysis of the somatic symptoms scale questionnaire showed a significant impact on 4 of the 8 subscales of symptoms: musculoskeletal ($F_{3, 36} = 2.855$; $p < 0.048$), cutaneous ($F_{3, 36} = 2.289$; $p < 0.050$), cardiovascular

Table 3. Analysis and effect sizes of the clinical variables

Measure	Group	T_0	p	T_3	p	T_9	p	T_{15}	p	Effect sizes		
										T_0–T_3	T_0–T_9	T_0–T_{15}
Symptoms[a]												
Cutaneous	TG	13.2 ± 4.6	0.518	11.9 ± 6.4	0.356	12.2 ± 7.6	0.976	10.4 ± 7.1	0.198	0.23	0.16	0.48
	CG	16.8 ± 8		16.4 ± 8		14.8 ± 7.8		16.5 ± 7.7		0.12	0.25	0.03
Musculoskeletal	TG	22.3 ± 7.2	0.872	19.6 ± 8.1	0.532	20 ± 9.7	0.932	18.3 ± 9.3	0.283	0.35	0.27	0.48
	CG	21.9 ± 8.1		21.3 ± 8.1		19.7 ± 10.1		21.6 ± 8.3		0.07	0.23	0.03
Cardiovascular	TG	11.8 ± 8.1	0.402	8.6 ± 6.4	0.701	9.5 ± 7.7	0.973	8 ± 6.6	0.496	0.28	0.29	0.51
	CG	9.7 ± 6.6		9.5 ± 7.1		9.4 ± 7.7		9.7 ± 7.2		0.02	0.04	0.00
Respiratory	TG	12.7 ± 7.3	0.524	10.4 ± 7.2	0.823	10.4 ± 8.4	0.973	9 ± 6	0.271	0.32	0.30	0.56
	CG	11.1 ± 7.9		10.9 ± 7.2		10.3 ± 7.9		11.7 ± 8.4		0.02	0.10	0.07
SLEDAI	TG	3.1 ± 3	0.466	2.6 ± 2.8	0.085	2.5 ± 3.2	0.268	2.6 ± 3.2	0.688	0.19	0.21	0.19
	CG	3.9 ± 2.9		4.6 ± 3.6		3.8 ± 3.3		3 ± 2.3		0.20	0.04	0.35
Flares/year	Year before therapy			Year after therapy						Year after–year before		
	TG	0.8 ± 1.1	0.196	1.1 ± 1.1	0.967					0.25		
	CG	0.4 ± 0.5		1.1 ± 1.4						0.80		

There were 21 patients in the TG and 24 in the CG. Values of effect sizes greater than 0.5 signify at least a moderate effect of the therapy on the reported variable.

[a] Symptoms were measured by a revised scale of somatic symptoms.

($F_{3, 41} = 3.216$; $p < 0.032$) and respiratory ($F_{3, 43} = 2.912$; $p < 0.047$). With regard to the immunological ($F_{3, 40} = 0.362$; $p < 0.765$), genitourinary ($F_{3, 40} = 1.333$; $p < 0.268$), neurological ($F_{3, 40} = 1.675$; $p < 0.189$) and gastrointestinal ($F_{3, 40} = 0.512$; $p < 0.635$) symptoms, no evidence of a significant impact of therapy was found. Later, neither the between-group nor within-group analyses showed statistically significant reductions in the general manifestation of reported symptoms either in the TG or in the CG.

Flares. There was no significant difference in the incidence of clinical flares during the year after the therapy when compared to the year before the study was carried out ($F_{1, 33} = 0.874$; $p < 0.357$).

QOL (SF-36)

The analysis showed a significant impact of the therapy on 5 of the 8 subscales: physical role ($F_{3, 39} = 2.778$; $p < 0.050$), pain ($F_{3, 39} = 4.758$; $p < 0.013$), social function ($F_{3, 39} = 3.431$; $p < 0.044$), mental health ($F_{3, 39} = 3.859$; $p < 0.023$) and general health ($F_{3, 39} = 3.248$; $p < 0.048$). There was no significant impact on physical function ($F_{3, 39} = 0.236$; $p < 0.856$), emotional role ($F_{3, 39} = 0.539$; $p < 0.584$) or vitality ($F_{3, 39} = 1.657$; $p < 0.159$). Later on, the only difference identified in the between-group analysis with Bonferroni correction was in physical role, as shown in table 2. No difference was identified in the within-group analysis.

Effect size estimates for each of the variables are provided in tables 2 and 3. A moderate effect size of at least 0.5 represents a clinically significant improvement [43]. Moderate to large effect sizes were found for the TG with regard to vulnerability to stress, perception of stress, anxiety, depression, social function, mental health and general health before and after treatment. Effect sizes were less than 0.5 in control conditions for all variables.

Discussion

This paper addresses a critically important issue, namely the effectiveness of cognitive-behavioural intervention in improving psychosocial stress and enhancing the well-being of individuals with lupus, using a randomized, prospective study. The results suggested that the intervention significantly reduced stress, anxiety and depression, considerably improved the QOL and reduced some somatic symptoms. The intensity of the effects was verified by moderate to large effect sizes following therapy and until the end of the study. There were no significant differences in the disease activity level measured using SLEDAI.

With regard to the emotional variables, it should be highlighted that, in addition to initially high levels of

chronic stress, the patients showed levels of anxiety that were higher than the average in the general Spanish population [39] and moderate levels of depression [44]. After therapy, levels of anxiety and depression among patients treated with CBT were considerably lower and even fell below the population average. Furthermore, these levels were maintained until the end of the study. Greco et al. [25] introduced a cognitive-behavioural stress reduction technique over 6 weeks to a group of patients with SLE and chronic pain. The authors described an improvement in perceived stress and levels of depression (measured by the Center for Epidemiologic Studies Depression Scale) after 9 months. Given that there are other factors besides pain that can produce stress, we included a more representative sample of patients with and without pain, so that the results could be easily generalized. The therapy used in our study focused on coping with stress in general and included the development of strategies for resolving other common issues that have a significant impact on the lives of these patients (for example, family and social relationships). The inclusion of patients of both sexes in our study in a way that reflects the existing proportion of male and female lupus sufferers enables us to apply the results obtained to all patients with lupus and high levels of daily stress.

As far as the clinical variables are concerned, there were no significant differences between the 2 groups in the level of disease activity (SLEDAI) during the 15-month follow-up. The low SLEDAI values at the beginning of the study could be, among others, one of the reasons for the lack of statistical differences. The lack of variability in the SLEDAI was a common finding in other studies which evaluated the efficacy of other psychotherapeutic interventions with different objectives, such as stress reduction [25, 45], limiting the interference of the disease in daily life [17] or improving social support [18]. Aside from disease activity, we did not find any significant differences in the perception of somatic symptoms between the 2 groups.

The physical role (SF-36) of patients who received the therapy improved. They experienced fewer physical or emotional problems in their daily lives. The improvements in general health, mental health and social function for the TG were not statistically significant.

The level of disease activity estimated by the doctor, based on clinical and analytical criteria, and the level estimated by the patient, who describes more or less activity depending on their physical and psychological well-being [46], often do not coincide. For this reason, some authors consider the analytical-clinical measures to be insufficient and believe that establishing QOL is possibly of more interest when analysing the impact of the disease [47]. For these patients, coping with stress could have an impact on their QOL. Specifically, as Rinaldi et al. [48] suggested, passive attitudes when faced with problems and the perception that situations cannot be changed reduced the QOL. This, together with the fact that patients with lupus usually have fewer coping strategies than the general population, and often less effective ones [49], supports our results that indicate that therapy has a beneficial effect on the QOL of patients. The introduction of therapy from the moment of initial diagnosis could be useful, given that patients may need to know how to cope with stress more effectively at that time.

Although this study meets the essential research criteria [50], it has some limitations. Given the low prevalence of this disease, the casuistry in this type of study is often relatively limited, which can affect the statistical strength and generalized application of results. The limited size of the sample in our study could partly explain the lack of long-term significance in the SLEDAI results. On the other hand, it is possible that starting the booster sessions a short time after the therapy sessions ended and increasing their frequency could have contributed to maintaining the significant differences between the 2 groups even after the therapy had finished.

The improvements found in somatic symptoms among the TG suggest that CBT therapy could make coping with the disease easier and change patients' cognitive appraisals of symptoms. Furthermore, the impact of therapy on psychosocial aspects (depression, anxiety, perceived vulnerability to stress, perceived health) and QOL may have implications for longer-term health behaviours and health outcomes. Therefore, it is essential that stress, its psychological consequences and its negative impact on the lives of the patients are taken into consideration [27, 29, 51]. These preliminary results should be verified in further studies. If the findings are confirmed then this could signal a new, more effective approach to dealing with lupus, given that a comprehensive, overall view of these patients is necessary when treating the clinical and psychological aspects of the disease.

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References

1 Dostal C, Marek J, Moszkorzova L, Lacinova Z, Musilova L, Zvarova J: Effects of stress on serum prolactin levels in patients with systemic lupus erythematosus. Ann NY Acad Sci 2002;966:247–251.

2 Kozora E, Ellison MC, Waxmansky JA, Wamboldt FS, Patterson TL: Major life stress, coping styles and social support in relation to psychological distress in patients with systemic lupus erythematosus. Lupus 2005;14: 363–372.

3 Wekking EM, Vingerhoets AJ: Daily stressors and systemic lupus erythematosus: a longitudinal analysis – first findings. Psychother Psychosom 1991;55:108–113.

4 Adams SG, Dammers PM, Saia TL, Brantley PJ, Gaydos GR: Stress, depression and anxiety predict average symptom severity and daily symptom fluctuation in systemic lupus erythematosus. J Behav Med 1994;17:459–477.

5 Schubert C, Lampe A, Rumpold G, Fuchs D, König P, Chamson E, Schatz D, König P, Fuchs D, Schüssler G: Daily psychosocial stressors interfere with the dynamics of urine neopterin in a patient with systemic lupus erythematosus: an integrative single-case study. Psychosom Med 1999;6:876–882.

6 Schubert C, Lampe A, Geser W, Noisternig B, Fuchs D, Konig P, Chamson E, Schüssler G: Daily psychosocial stressors and cyclic response patterns in urine cortisol and neopterin in a patient with systemic lupus erythematosus. Psychoneuroendocrinology 2003; 28:459–473.

7 Schubert C, Geser W, Noisternig B, Konig P, Rumpold G, Lampe A: Stressful life events and skin diseases: An additional perspective from research on psychosomatic dynamics in systemic lupus erythematosus. Psychother Psychosom 2002;71:123–126.

8 Peralta-Ramírez MI, Jiménez-Alonso J, Godoy-García JF, Pérez-Garcia M: The effects of daily stress and stressful life events on the clinical symptomatology of patients with lupus erythematosus. Psychosom Med 2004; 66:788–794.

9 Pawlack CR, Witte T, Heiken H, Hundt M, Schubert J, Wiese B, Bischoff-Renken A, Gerber K, Licht B, Goebel MU, Heijnen CJ, Schmidt RE, Schedlowski M: Flares in patients with systemic lupus erythematosus are associated with daily psychological stress. Psychother Psychosom 2003;72:159–165.

10 Peralta-Ramírez MI, Coín-Mejías MA, Jiménez-Alonso J, Ortego-Centeno N, Callejas-Rubio JL, Caracuel-Romero A, Pérez-García M: Stress as a predictor of cognitive functioning in lupus. Lupus 2006;15:858–864.

11 Herrmann M, Scholmerich J, Straub RH: Stress and rheumatic diseases. Rheum Dis Clin North Am 2000;26:737–763.

12 Wilder RL: Neuroimmunoendocrinology of the rheumatic diseases: past, present and future. Ann NY Acad Sci 2002;966:13–19.

13 Van Hout MS, Wekking EM, Berg IJ, Deelman BG: Psychosocial and cognitive rehabilitation of patients with solvent-induced chronic toxic encephalopathy: a randomised controlled study. Psychother Psychosom 2008;77:289–297.

14 Andersen BL, Yang HC, Farrar WB, Golden-Kreutz DM, Emery CF, Thornton LM, Young DC, Carson WE 3rd: Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. Cancer 2008;113:3450–3458.

15 Busse JW, Montori VM, Krasnik C, Patelis-Siotis I, Guyatt GH: Psychological intervention for premenstrual syndrome: a meta-analysis of randomized controlled trials. Psychother Psychosom 2009;78:6–15.

16 Janeway D: An integrated approach to the diagnosis and treatment of anxiety within the practice of cardiology. Cardiol Rev 2009;17: 36–43.

17 Edworthy SM, Dobkin PL, Clarke AE, Da Costa D, Dritsa M, Fortin PR, Barr S, Ensworth S, Esdaile JM, Beaulieu A, Zummer M, Senécal JL, Goulet JR, Choquette D, Rich E, Smith D, Cividino A, Gladman D, Devins GM: Group psychotherapy reduces illness intrusiveness in systemic lupus erythematosus. J Rheumatol 2003;30:1011–1016.

18 Karlson EW, Liang MH, Eaton H, Fitzgerald L, Rogers MP, Daltroy LH: A randomized clinical trial of a psychoeducational intervention to improve outcomes in systemic lupus erythematosus. Arthritis Rheum 2004; 50:1832–1841.

19 Braden CJ, McGlone K, Pennington F: Specific psychosocial and behavioral outcomes from the systemic lupus erythematosus self-help course. Health Educ Q 1993;20:29–41.

20 Sohng KY: Effects of a self-management course for patients with systemic lupus erythematosus. J Adv Nurs 2003;42:479–486.

21 Haupt M, Millen S, Jänner M, Falagan D, Fischer-Betz R, Schneider M: Improvement of coping abilities in patients with systemic lupus erythematosus: a prospective study. Ann Rheum Dis 2005;64:1618–1623.

22 Rhee SH, Parker JC, Smarr KL, Petroski GF, Johnson JC, Hewett JE, Wright GE, Multon KD, Walker SE: Stress management in rheumatoid arthritis: what is the underlying mechanism? Arthritis Care Res 2000;13: 435–442.

23 Van Lankveld W, van Helmond T, Naring G, de Rooij DJ, van den Hoogen F: Partner participation in cognitive-behavioral self-management group treatment for patients with rheumatoid arthritis. J Rheumatol 2004;31: 1738–1745.

24 Eich W, Blumenstiel K, Lensche H, Fiehn C, Bieber C: Psychosomatics in rheumatology (in German). Z Rheumatol 2004;63:113–121.

25 Greco CM, Rudy TH, Manzi S: Effects of a stress-reduction program on psychological function, pain and physical function of systemic lupus erythematosus patients: a randomized controlled trial. Arthritis Rheum 2004;51:625–634.

26 Jennekens FG, Kater L: The central nervous system in systemic lupus erythematosus. 1. Clinical syndromes: a literature investigation. Rheumatology (Oxford) 2002;41:605–618.

27 Seawell AH, Danoff-Burg S: Psychosocial research on systemic lupus erythematosus: a literature review. Lupus 2004;13:891–899.

28 Segui J, Ramos-Casals M, García-Carrasco M, de Flores T, Cervera R, Valdés M, Font J, Ingelmo M: Psychiatric and psychosocial disorders in patients with systemic lupus erythematosus: a longitudinal study of active and inactive stages of the disease. Lupus 2000;9:584–588.

29 Moses N, Wiggers J, Nicholas C, Cockburn J: Prevalence and correlates of perceived unmet needs of people with systemic lupus erythematosus. Patient Educ Couns 2005;57: 30–38.

30 Dobkin PL, Da Costa D, Dritsa M, Fortin PR, Senecal JL, Goulet JR, Choquette D, Rich E, Beaulieu A, Cividino A, Edworthy S, Barr S, Ensworth S, Esdaile JM, Gladman D, Smith D, Zummer M, Clarke AE: Quality of life in systemic lupus erythematosus patients during more and less active disease states: differential contributors to mental and physical health. Arthritis Care Res 1999;12:401–410.

31 Doria A, Rinaldi S, Ermani M, Salaffi F, Iaccarino L, Ghirardello A, Zampieri S, Della Libera S, Perini G, Todesco S: Health-related quality of life in Italian patients with systemic lupus erythematosus. II. Role of clinical, immunological and psychological determinants. Rheumatology (Oxford) 2004; 43:1580–1586.

32 Cohen S, Kamarck T, Mermelstein R: A global measure of perceived stress. J Health Soc Behav 1983;24:385–396.

33 Remor E: Psychometric properties of a European Spanish version of the Perceived Stress Scale (PSS). Span J Psychol 2006;9:86–93.

34 Robles-Ortega H, Peralta-Ramírez MI: Programa para el control del estrés. Madrid, Pirámide, 2006.

35 Beech HR, Burns LE, Sheffield BF: A Behavioral Approach to the Management of Stress: A Practical Guide to Techniques. Chichester, Wiley, 1982.

36 Robles H, Peralta MI, Navarrete N: Validación de la versión española del inventario de vulnerabilidad al estrés de Beech, Burn y Sheffield; in Facultad de Ciencias Médicas 'Doctor Raúl Dorticós Torrado' (ed): Avances en Psicología de la Salud. Cienfuegos, Sider, 2006, p 62.

37 Kohn PM, MacDonald JE: The Survey of Recent Life Experiences: a decontaminated Hassles Scale for adults. J Behav Med 1992; 15:221–236.
38 Beck AT, Steer RA, Garbin MG: Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psychol Rev 1988;8:77–100.
39 Spielberger CD, Gorsuch RL, Lushene RE: STAI. Cuestionario de Ansiedad Estado-Rasgo. Madrid, TEA, 1993.
40 Ware JE, Sherbourne CD: The MOS 36-item Short Form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–483.
41 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH: Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35: 630–640.
42 Sandín B, Chorot P, Santed MA, Jiménez MP: Trastornos psicosomáticos; in Belloch A (ed): Manual de psicopatología. Madrid, McGraw-Hill, 1995, pp 401–469.
43 Cohen J: Statistical Power Analysis for the Behavioral Sciences, ed 2. Hillsdale, Lawrence Erlbaum, 1988.
44 Vázquez C, Sanz J: Fiabilidad y valores normativos de la versión española del inventario para la depresión de Beck de 1978. Clin Salud 1997;8:403–422.
45 Greco CM, Rudy TE, Manzi S: Effects of disease activity, pain and distress on activity limitations in patients with systemic lupus erythematosus. J Rheumatol 2004;31:260–267.
46 Yen JC, Abrahamowicz M, Dobkin PL, Clarke AE, Battista RN, Fortin PR: Determinants of discordance between patients and physicians in their assessment of lupus activity. J Rheumatol 2003;30:1967–1976.
47 Khanna S, Pal H, Pandey RM, Handa R: The relationship between disease activity and quality of life in systemic lupus erythematosus. Rheumatology 2004;43:1536–1540.
48 Rinaldi S, Ghisi M, Iaccarino L, Zampieri S, Ghirardello A, Sarzi-Puttini P, Ronconi L, Perini G, Todesco S, Sanavio E, Doria A: Influence of coping skills on health-related quality of life in patients with systemic lupus erythematosus. Arthritis Rheum 2006;55: 427–433.
49 Schwartz CE, Peng CK, Lester N, Daltroy LH, Goldberger AL: Self-reported coping behavior in health and disease: assessment with a card sort game. Behav Med 1998;24: 41–44.
50 Basler HD, Kaluza G, Lledó-Boyer A: Evaluación de un programa de salud de afrontamiento al estrés. Ansiedad Estres 2003;9: 85–91.
51 Schattner A, Naparstek Y: The future of the treatment of systemic lupus erythematosus. Clin Exp Rheumatol 2005;23:254–260.