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Psychological Morbidity, Fatigue and Burden of Disease in Patients With Connective Tissue Diseases

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ABSTRACT

Objective: Depression and anxiety disorders are significant health problems that can coexist with other diseases and exert adverse effects on these diseases' course and treatment response. Fatigue is a common and disabling symptom in chronic inflammatory diseases. The present study aimed to evaluate the fatigue, anxiety, depression and burden of disease (eg, disease activity, function, quality of life) in autoimmune connective tissue disease (CTD) patients.

Methods: 160 patients diagnosed with CTD and 50 healthy control patients were included in the present study. Disease activity scores were recorded. All patients were asked to fill the Short Form-36, Fatigue Severity Scale, Hospital Depression and Anxiety Scale (HADS).

Results: In all patients groups, anxiety, depression, and fatigue scores were significantly higher, and quality of life scores significantly lower than those of healthy controls. A significant positive correlation was found between rheumatoid arthritis activity, HADS anxiety and depression scores. It was also established that in scleroderma patients with diffuse skin involvement and pulmonary involvement, depression and anxiety scores were high.

Conclusion: It is clear that psychiatric comorbidity and fatigue may be present in CTD and adversely affects quality of life. It is important to assess them and they should be an important treatment target.

Keywords: Anxiety, connective tissue diseases, depression, fatigue, quality of life

1. INTRODUCTION

In patients with connective tissue diseases (CTD), comorbid depression and anxiety prevalence are 2 to 4-fold higher than the general population (1, 2). Although its exact etiology is unknown, it has been demonstrated that physical symptoms, physical limitations, pro-inflammatory cytokines, and other factors related to having the chronic disease are associated with depression (1). It is thought that fatigue may be more marked in these patient groups, and the inflammatory process, which becomes more intensive inactive disease periods, may further increase fatigue (3). Important points that are stressed in the pathophysiology of fatigue are autonomous dysfunction, sympathetic overactivation, decrease in brain volume, CRH release defect, cytokines and immune reactivation, and defects in central neurotransmitter release. Fatigue, anxiety, and depression may lead to a reduction in physical activity and compliance with treatment, which may result in aggravation of the disease and worse health outcomes. Adequate CTD treatment influencing well-being and quality of life in patients may decrease the risk of such comorbid conditions (4).

Although fatigue, anxiety, and depression have been studied separately in each CTD patient, few results examine this in all connective tissue diseases. Therefore, this study aimed to evaluate fatigue, anxiety, depression, and burden of disease (disease activity, function, quality of life) in CTD patients.

2. MATERIALS AND METHODS

2.1. Study Population and Design

The study included 160 consecutive patients with CTD, who were admitted to Rheumatology outpatient clinic, and 50 healthy volunteers admitted to routine health follow-up outpatient clinic between October 2020 and January 2021. The study group included 30 patients with systemic sclerosis (SSc), 30 patients with Sjögren's syndrome (SS), 30 patients with Systemic Lupus Erythematosus (SLE), 70 patients with

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rheumatoid arthritis. Those with a chronic neurological disease, history of head trauma, or the central nervous system, metabolic or endocrinological disease, known psychiatric disorder, alcohol and/or substance abuse, and those who are on drugs that can lead to depression were excluded from the study. All procedures complied with the 1964 Declaration of Helsinki ethical standards. The study was approved by the Ethics Committee with the decision dated 30.09.2020 and numbered 220/419.

2.2 Assessment of Laboratory Markers and Clinical Parameters in Patients with CTD

In all patients, demographic (age, sex, marital status, education level, work status) and clinical data (the type of disease, duration of disease, organ involvement, disease activity, drugs used, immunological evaluation, physical examination, and laboratory tests) were recorded. Erythrocyte sedimentation rate (ESH) was measured with the Westergren method (mm/h) and serum C-reactive protein (CRP) levels with nephelometer(mg/dl).

2.3. Definition and Assessment of Clinical Scores in Patients with CTD

In order to evaluate disease activity in each patient group, for SLE patients SLEDAI (Systemic Lupus Erythematosus Disease Activity İndex), for RA patients, DAS28 (Disease Activity Score) and for SS, EULAR SS Disease Activity Index (ESSDAI) were used. For SSc, skin and pulmonary involvement degree was determined. DAS28 was interpreted as follows: <2.6: remission, >2.6 and <=3.2: low disease activity, >3.2 and <=5.1: moderate disease activity, >5.1: High disease activity. SLEDAI score range was interpreted as follows: 0-1: no activity; 1-5, mild activity; 6-10, moderate activity; 11–19, high activity and ≥20 very high activity. Low moderate, and high activity was defined as respectively ESSDAI scores of <5, 5-13, and ≥ 14.

2.4. Assessment of Quality of Life (QoL) and Functional Status in Patients with CTD

To measure both physical and mental components of HRQoL, we utilized the Short Form-36 (SF-36), a robust and accurate questionnaire. The SF-36 comprises 36 elements that are organized into eight dimensions (5). These subscales are physical functioning (PP) role limitations due to physical problems (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Scores vary between 0-100 points, with 100 indicating the best quality of life and 0 the worst.

2.5. Assessment of Anxiety and Depression in Patients with CTD

The Hospital Anxiety and Depression Scale (HADS) is a self-reported questionnaire to assess and measure the risk of depression and/or anxiety. HADS is a reliable and validated psychological scale that consists of 14 questions; half of them evaluate anxiety and the others evaluate depression with four probable responses (score 0–3). A score over 8 points is accepted as the presence of anxiety and depression. In accordance with the HADS Turkish validation study, if scores ≥11 acknowledged as anxiety, and ≥8 accepted as depression in the present study (6).

2.6. Assessment of Fatigue in Patients with CTD

The Fatigue Security Scale (FSS), valid in Turkish, is a self-reported questionnaire consisting of 9 items, each ranging from 1 to 7 points in a Likert scale, was used to evaluate the severity of fatigue in various situations (motivation, exercise, physical functioning, carrying out duties, interference with work, family, or social life) during the past week (3). FSS final score 4 was interpreted as fatigue (7).

2.7. Statistical Analysis

Statistical analyses were conducted with R (version 3.6.0., The R Project for Statistical Computing, https://www.r-project.org). Shapiro-Wilk's test and Q-Q plots were used to assess the normality, and Levene's test was used to check the homogeneity of variance. Quantitative variables were presented as mean ± standard deviation or median (interquartile range), and qualitative variables were described as counts (n) and percentages (%). One-Way ANOVA (one-way analysis of variances) followed by Tukey HSD (honestly significant difference) post-hoc test, Kruskal Wallis test followed by Dunn post-hoc test using Bonferroni correction, and Chi-square test was used to compare the study groups according to the demographic characteristics, laboratory findings, disease activity scores, FSS, anxiety and depression scores, and SF36 scores. Moreover, Spearman's rho correlation test was used to define the relationship between RA, SLE, and SS diseases' activity scores and FSS score, HADS score and SF36, and also, student's t-test, Welch's t-test, and Mann-Whitney U test were run to analyze the differences between SSc and these scores. Also, univariate binary logistic regression analysis was carried out to identify the risk factors of anxiety and depression for each disease group. Fisher's exact test and Yates continuity correction were used to calculating the p-value of SSc in anxiety and depression, respectively, and the odds ratio was calculated with 2×2 crosstabs. The significance level was set at 5%.

3. RESULTS

210 participants were included in the present study. Of these, 169 were female and 41 males. Demographic characteristics of patients, laboratory results, disease activity scores, FSS, HAD anxiety and depression scores, and SF36 scores are illustrated in Table 1. There was no significant difference between disease groups with respect to age, duration of disease, and smoking status, while in a control group, the rate of females and married patients was lower than disease groups. There

was a significant relation between FSS, HADS-A, HADS-D, and SF36 scores. For each disease, factors that can influence the anxiety and depression levels of patients are showed in Table 3. The Depression and anxiety level of patients with each disease compared to healthy controls was shown in Table 3. In the comparison of HADS-A and HADS-D scores, anxiety and depression scores were found to be significantly higher in CTD patients than healthy controls (Figure 1). FFS score was higher in all patient groups than the control group. SF 36 subscale scores were markedly lower in all patient groups than healthy controls. RA patients had lower SF36 scores, with a pronounced decrease in RP and RE subscales.

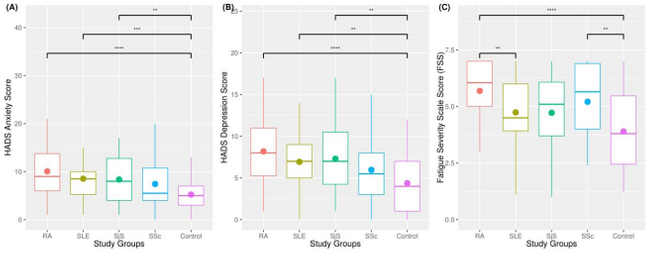

Figure 1. *The comparisons of HADS Anxiety Score, HADS Depression Score and Fatigue Severity Scale Score (FSS) in study groups.*

In RA patients, HADS-D was found to be 8 (5.25–11) and HADS-A was 9 (6 – 13.75). According to these results, it was established that in RA patients, anxiety risk was 5.646 (2.476–12.874) fold higher and depression risk 4.750 (2.121 – 10.636) fold higher than healthy subjects. There was a significant positive relation between DAS28 CRP, ESH and FSS, and HADS anxiety and depression scores, whilst a significant negative correlation was found with SF36 parameters. Besides, in RA patients, an increase in FSS score increased anxiety risk 1.516 (1.048–2.194) fold and depression risk 1.714 (1.156 – 2.542) fold, which was significant (p=.027 and p=.007, respectively). It was found that a rise in DAS28 – CRP, increased the risk of anxiety 1.653 (1.074 – 2.544) fold and risk of depression 2.963 (1.717–5.113) fold. (p=.022 and p<.001, respectively). Besides, in patients who have active disease according to DAS28 CRP, the risk of anxiety was 3.173 (1.165–8.641) fold and risk of depression 8.455 (2.821 – 25.339) fold higher than those who are in remission. (p=.024 and p<.001, respectively). It was also determined that in the SF36 scale, an increase in RP, RE, VT, MH, SF, and GH values significantly correlated with anxiety, whereas PF and BP had no impact on anxiety. However, a negative correlation was observed between all subscales of SF-36 and depression.

It was found that while in SLE patients, anxiety risk was 6.124 (2.254 – 16.639) times as high as healthy subjects, there was no difference in depression risk. (p=.074). No significant relation was found between SLEDAI scores and FSS, HADS, and SF36 parameters. It was determined that in SLE patients, a rise in FSS score significantly increased anxiety risk 2.961 (1.233 – 7.107) fold and depression risk 2.304 (1.131 – 4.697) fold (p=.015 and p=.022, respectively). SLEDAI scores were found to exert no effect on anxiety and depression levels. (p>.05). An increase in SF36 PF, RP, RE, and GH subscale values was found to decrease anxiety significantly, while VT, MH, SF, and BP had no effect on anxiety. As to depression, it was determined that an increase in SF36 RT, RE, and MH values decreased depression while other SF36 parameters exerted no significant effect on depression.

It was established that in SS patients, anxiety risk was 3.545 (1.331-9.444) times and depression risk 2.771 (1.053-7.290) times higher than healthy subjects. No significant relation was found between ESSDAI scores and FSS, HADS, and SF36 parameters. It was established that ESSDAI scores had no impact on anxiety and depression. (p>.05). Among SF36 parameters, an increase in VT, MH, SF, and GH scores was found to decrease anxiety significantly, and an increase in PF, RP, RE, SF, and GH scores reduced depression significantly. In addition, it was also established that in SS patients, the FSS score exerted no effect on anxiety while an increase in this score increased the risk of depression 2.304 (1.131 – 4.697) fold (p=.167 and p=.019, respectively).

SSc patients were found to be similar to healthy subjects in terms of anxiety and depression risk (p=.089 and p=.556, respectively). The relation between SSc and FSS, HADS, and SF36 parameters are demonstrated in Table 2. In SSc cases, patients with diffuse skin involvement (dcSSC) were found to have a significantly higher mean HADS anxiety score (9.44 ± 5.32) than those with limited skin involvement (lcSSC) (4.42 ± 2.23). (p=.002). However, it was established that patients with dcSSC and pulmonary involvement had significantly higher mean HADS scores (7.33 ± 4.58 and 7.24 ± 5.03, respectively) than those with lcSSC and without pulmonary involvement (3.92 ± 2.68 and 4.31 ± 2.06, respectively). (p=.027 and p=.041, respectively). Also, dcSSC were found to have significantly lower SF36 MH scores (56.44 ± 17.67) than those with lcSSC (72.67± 14.05) (p=.013). Besides, lcSSC were found to have a 95.8 % lower risk of anxiety than those with dcSSC (OR=0.058, 95% CI=0.006 – 0.552, p=.013). Nevertheless, the effect of skin involvement status on depression was not significant. (p=.114). Patients without pulmonary involvement were found to have a 96.7% lower risk of depression than those without pulmonary involvement. (OR=0.033, 95% CI=0.002-0.646, p=.003). An increase in FSS score in SSc patients was established to increase the risk of depression by 2.499 (1.118-5.587) fold (p=.026). Finally, an increase in SF36 parameters of VT, MH, and SF decreased the risk of anxiety, while an increase in PF, RP, MH, SF, BP, and GH decreased the risk of depression.

Table 1. *Demographics characteristics, laboratory findings, disease activity scores, FSS, HADS and SF36 scores in study groups*

	Control (*n*=50)	RA (*n*=70)	SLE (*n*=30)	SjS (*n*=30)	SSc (*n*=30)	*p*-value
Demographics						
Age (years)	46.52 ± 9.82	49.63 ± 10.28	43.37 ± 12.72	50.10 ± 8.52	47.23 ± 12.83	.057
Female gender	27 (54)	61 (87.1)	25 (83.3)	27 (90)	29 (96.7)	**<.001**
Disease duration (years)	NA	4 (2 – 8)	5.5 (4 – 10)	5 (2 – 7)	5 (2.25 – 7)	.333
Marital status (married)	15 (30)	66 (94.3)	22 (73.3)	28 (93.3)	26 (86.7)	**<.001**
Smoking	16 (32)	8 (11.4)	8 (26.7)	9 (30)	5 (16.7)	.051
Laboratory findings						
CRP	NA	8 (4 – 15.75)[a]	2.60 (1.90 – 3.30)[b]	4 (2.85 – 5)[b]	3.80 (2.05 – 6.45)[b]	**<.001**
ESH	NA	22 (12.25 – 38.75)	14 (6 – 21)	15 (8 – 27.25)	17.5 (11.5 – 29.25)	.088
Disease activity scores						
DAS28-CRP score		2.99 ± 1.23				
DAS28-CRP level						
Remission (<2.6)		32 (45.7)				
Low activity (>2.6 and ≤3.2)		7 (10)				
Moderate activity (>3.2 and ≤5.1)		28 (40)				
High activity (>5.1)		3 (4.3)				
DAS28-ESR score		3.79 ± 1.39				
DAS28-ESR level						
Remission (<2.6)		17 (24.3)				
Low activity (>2.6 and ≤3.2)		11 (15.7)				
Moderate activity (>3.2 and ≤5.1)		29 (41.4)				
High activity (>5.1)		13 (18.6)				
SLEDAI score			14.90 ± 8.86			
SLEDAI level						
No activity (0)			0 (0)			
Mild activity (1–5)			3 (10)			
Moderate activity (6–10)			6 (20)			
High activity (11–19)			14 (46.7)			
Very high activity (≥20)			7 (23.3)			
ESSDAI score				5.73 ± 4.01		
ESSDAI level						
Low activity (<5)				16 (53.3)		
Moderate activity (5–13)				11 (36.7)		
High activity (≥14)				3 (10)		
Kutanöz involvement						
dcSSc					18 (60)	
lcSSc					12 (40)	
Pulmoner involvement						
Absent					13 (43.3)	
Present					17 (56.7)	
FSS	3.80 (2.45 – 5.47)[a]	6.05 (5 – 7)[b]	4.50 (3.92 – 6)[ac]	5.10 (3.70 – 6.07)	5.65 (4 – 6.90)[bc]	**<.001**
Anxiety and depression scores						
HADS anxiety score	5 (3 – 7)[a]	9 (6 – 13.75)[b]	8.5 (5.25 – 10)[b]	8 (4 – 12.75)[b]	5.5 (4 – 10.75)	**<.001**
HADS anxiety level						**<.001**
Absent (<8)	39 (78)	27 (38.6)	11 (36.7)	15 (50)	18 (60)	
Possible (8–10)	8 (16)	16 (22.9)	13 (43.3)	2 (6.7)	4 (13.3)	
Probable (11–14)	3 (6)	13 (18.6)	2 (6.7)	10 (33.3)	4 (13.3)	
Extreme (15–21)	0 (0)	14 (20)	4 (13.3)	3 (10)	4 (13.3)	
HADS depression score	4 (1 – 7)[a]	8 (5.25 – 11)[b]	7 (5 – 9)[b]	7 (4.25 – 10.5)[b]	5.5 (3 – 8)	**<.001**
HADS depression level						**.013**
Absent (<8)	38 (76)	28 (40)	17 (56.7)	16 (53.3)	21 (70)	
Possible (8–10)	10 (20)	23 (32.9)	9 (30)	6 (20)	6 (20)	
Probable (11–14)	2 (4)	14 (20)	4 (13.3)	6 (20)	1 (3.3)	
Extreme (15–21)	0 (0)	5 (7.1)	0 (0)	2 (6.7)	2 (6.7)	
Short form (36) heath survey (SF36)						
SF36-PF	90 (80 – 100)[ac]	50 (21.25 – 75)[b]	80 (56.25 – 98.75)[c]	57.5 (42.5 – 98.75)[bc]	60 (45 – 85)[bc]	**<.001**
SF36-RP	100 (100 – 100)[a]	0 (0 – 100)[b]	100 (6.25 – 100)	75 (0 – 100)[b]	12.5 (0 – 75)[b]	**<.001**
SF36-RE	100 (100 – 100)[a]	0 (0 – 91.67)[b]	100 (0 – 100)	100 (0 – 100)	66.67 (0 – 100)	**<.001**
SF36-VT	59.10 ± 21.01[ac]	36.07 ± 18.37[b]	49.67 ± 20.21[c]	40.50 ± 17.14[bc]	45.33 ± 23.15[bc]	**<.001**
SF36-MH	70.48 ± 16.10[a]	55.20 ± 18.29[b]	63.47 ± 13.44	58.93 ± 17.89[b]	62.93 ± 17.98	**<.001**
SF36-SF	75 (50 – 100)[a]	50 (37.5 – 62.5)[b]	75 (50 – 87.5)[a]	62.5 (50 – 84.38)	62.5 (37.5 – 87.5)	**<.001**
SF36-BP	90 (77.5 – 100)[ac]	45 (22.5 – 67.5)[b]	77.5 (55 – 90)[c]	67.5 (37.5 – 77.5)[bc]	61.25 (45 – 77.5)[bc]	**<.001**
SF36-GH	71.06 ± 16.73[a]	36.79 ± 15.74[b]	47 ± 21.03[b]	45.30 ± 16.86[b]	46.50 ± 20.68[b]	**<.001**

Data were expressed as mean ± standard deviation or median (interquartile range).Bold values indicate that statistically significance (p<.05). [a,b,c] Each different superscript letters in each row indicate that statistically significant difference between groups.p-values calculated using One-Way ANOVA with Tukey HSD, Kruskal Wallis test with Dunn-Bonferroni post-hoc test, or Chi-square test, as appropriate..Abbreviations: RA: Rheumatoid Arthritis, SjS: Sjogren's Syndrome, SLE: Systemic Lupus Erythematosus, SSc: Systemic Sclerosis, FSS: Fatigue severity scale, HADS anxiety and HADS depression: Hospital anxiety and depression scale, SF36: Short form health survey, PF: Physical function, RP: Role limitations due to physical health, RE: Role limitations due to emotional problems, VT: Energy/fatigue, MH: Mental health, SF: Social function, BP: Bodily pain, GH: General health

Table 2. *Relationship between RA, SLE and SjS diseases' activity scores and FSS score, HADS score and SF36, and also differences between SSc and these scores.*

	RA (*n*=70)		SLE (*n*=30)	SjS (*n*=30)	SSc (*n*=30)			
		DAS28	SLEDAI	ESSDAI		Diffuse/Present	Limited/Absent	*p*-value
FSS			0.028 (.885)	0.289 (.122)				
	CRP	0.629 (**<.001**)			Kutanöz	5.29 ± 1.65	5.09 ± 1.47	.741[a]
	ESR	0.489 (**<.001**)			Pulmoner	5.42 ± 1.59	4.93 ± 1.52	.400[a]
HADS								
HADS anxiety			–0.154 (.418)	–0.008 (.967)				
	CRP	0.351 (**.003**)			Kutanöz	9.44 ± 5.32	4.42 ± 2.23	**.002**[b]
	ESR	0.255 (**.033**)			Pulmoner	8.76 ± 5.78	5.69 ± 3.07	.073[b]
HADS depression			0.042 (.826)	0.153 (.421)				
	CRP	0.547 (**<.001**)			Kutanöz	7.33 ± 4.58	3.92 ± 2.68	**.027**[a]
	ESR	0.513 (**<.001**)			Pulmoner	7.24 ± 5.03	4.31 ± 2.06	**.041**[b]
SF36								
SF36-PF			0.206 (.274)	0.045 (.813)				
	CRP	–0.576 (**<.001**)			Kutanöz	57.22 ± 26.58	66.67 ± 26.57	.348[a]
	ESR	–0.551 (**<.001**)			Pulmoner	57.35 ± 26.64	65.77 ± 26.68	.399[a]
SF36-RP			0.322 (.082)	0.011 (.955)				
	CRP	–0.556 (**<.001**)			Kutanöz	12.50 (0 – 75)	25 (0 – 75)	.964[c]
	ESR	–0.508 (**<.001**)			Pulmoner	0 (0 – 75)	50 (0 – 75)	.892[c]
SF36-RE			0.169 (.372)	–0.135 (.478)				
	CRP	–0.477 (**<.001**)			Kutanöz	83.34 (0 – 100)	50 (0 – 100)	.597[c]
	ESR	–0.403 (**<.001**)			Pulmoner	66.67 (0 – 100)	100 (0 – 100)	.555[c]
SF36-VT			–0.002 (.992)	–0.135 (.478)				
	CRP	–0.514 (**<.001**)			Kutanöz	40.28 ± 21.45	52.92 ± 24.44	.146[a]
	ESR	–0.482 (**<.001**)			Pulmoner	43.53 ± 24.61	47.69 ± 21.85	.634[a]
SF36-MH			–0.045 (.812)	–0.074 (.698)				
	CRP	–0.484 (**<.001**)			Kutanöz	56.44 ± 17.67	72.67 ± 14.05	**.013**[a]
	ESR	–0.369 (**.002**)			Pulmoner	59.29 ± 20.51	67.69 ± 13.31	.186[b]
SF36-SF			0.286 (.125)	–0.039 (.837)				
	CRP	–0.380 (**<.001**)			Kutanöz	59.03 ± 27.05	69.79 ± 27.93	.301[a]
	ESR	–0.330 (**.005**)			Pulmoner	61.03 ± 20.51	66.35 ± 25.71	.608[a]
SF36-BP			0.251 (.182)	0.195 (.301)				
	CRP	–0.533 (**<.001**)			Kutanöz	56.53 ± 21.46	69.17 ± 24.57	.147[a]
	ESR	–0.508 (**<.001**)			Pulmoner	59.26 ± 23.30	64.62 ± 23.67	.541[a]
SF36-GH			0.073 (.703)	–0.213 (.258)				
	CRP	–0.601 (**<.001**)			Kutanöz	32.50 (30 – 61.25)	60 (42.50 – 66.25)	.060[c]
	ESR	–0.536 (**<.001**)			Pulmoner	30 (30 – 50)	65 (35 – 65)	.073[c]

Data were expressed as mean ± standard deviation or median (interquartile range) for SSc, and presented as Spearman's rho (p-value) for RA, SjS and SLE. Bold values indicated that statistically significance (p<.05)

[a] *student's t test*

[b] *Welch's t test*

[c] *Mann-Whitney U test*

Abbreviations: RA: Rheumatoid Arthritis, SjS: Sjogren's Syndrome, SLE: Systemic Lupus Erythematosus, SSc: Systemic Sclerosis, FSS: Fatigue severity scale, HADS anxiety and HADS depression: Hospital anxiety and depression scale, SF36: Short form health survey, PF: Physical function, RP: Role limitations due to physical health, RE: Role limitations due to emotional problems, VT: Energy/fatigue, MH: Mental health, SF: Social function, BP: Bodily pain, GH: General health, DAS28-CRP: Disease activity score that uses c-reactive protein, DAS28-ERP: Disease activity score that uses erythrocyte sedimentation rate, ESSDAI: European league against rheumatism SS disease activity index, SLEDAI: Systemic lupus erythematosus disease activity index, dcSSc: Diffuse cutaneous scleroderma, lcSSc: Limited cutaneous scleroderma

Table 3. *Risk factors for the anxiety and depression in each disease group.*

	HADS Anxiety (≥8 vs <8)		HADS Depression (≥8 vs <8)	
	OR (%95 CI)	*p*-value	OR (%95 CI)	*p*-value
Rheumatoid Arthritis (vs control)	5.646 (2.476 – 12.874)	**<.001**	4.750 (2.121 – 10.636)	**<.001**
Age (years)	0.973 (0.926 – 1.022)	.272	0.953 (0.906 – 1.004)	.070
Disease duration (years)	0.990 (0.914 – 1.073)	.807	0.981 (0.905 – 1.062)	.635
CRP	1.029 (0.976 – 1.085)	.287	1.102 (1.023 – 1.187)	**.011**
ESH	1.006 (0.980 – 1.032)	.670	1.016 (0.989 – 1.044)	.243
FSS	1.516 (1.048 – 2.194)	**.027**	1.714 (1.156 – 2.542)	**.007**
SF36-PF	0.987 (0.972 – 1.002)	.088	0.983 (0.968 – 0.998)	**.031**
SF36-RP	0.984 (0.972 – 0.995)	**.005**	0.986 (0.975 – 0.997)	**.012**
SF36-RE	0.981 (0.970 – 0.993)	**.002**	0.975 (0.963 – 0.988)	**<.001**
SF36-VT	0.950 (0.920 – 0.982)	**.002**	0.932 (0.898 – 0.968)	**<.001**
SF36-MH	0.941 (0.908 – 0.976)	**<.001**	0.900 (0.854 – 0.948)	**<.001**
SF36-SF	0.954 (0.928 – 0.981)	**<.001**	0.952 (0.925 – 0.979)	**<.001**
SF36-BP	0.986 (0.968 – 1.004)	.129	0.976 (0.957 – 0.995)	**.015**
SF36-GH	0.955 (0.922 – 0.989)	**.010**	0.909 (0.867 – 0.952)	**<.001**
DAS28 CRP score	1.653 (1.074 – 2.544)	**.022**	2.963 (1.717 – 5.113)	**<.001**
DAS28 ESH score	1.362 (0.944 – 1.965)	.098	2.369 (1.487 – 3.772)	**<.001**
DAS28 CRP activity (vs remission)	3.173 (1.165 – 8.641)	**.024**	8.455 (2.821 – 25.339)	**<.001**
DAS28 ESH activity (vs remission)	3.025 (0.982 – 9.318)	.054	5.550 (1.677 – 18.368)	**.005**
Systemic Lupus Erythematosus (vs control)	6.124 (2.254 – 16.639)	**<.001**	2.422 (0.917 – 6.394)	.074
Age (years)	0.998 (0.941 – 1.059)	.952	0.981 (0.926 – 1.040)	.523
Disease duration (years)	0.874 (0.751 – 1.016)	.080	0.899 (0.772 – 1.047)	.171
CRP	1.059 (0.790 – 1.419)	.702	0.848 (0.594 – 1.210)	.364
ESH	1.006 (0.971 – 1.042)	.751	0.997 (0.965 – 1.031)	.868
FSS	2.961 (1.233 – 7.107)	**.015**	2.304 (1.131 – 4.697)	**.022**
SF36-PF	0.953 (0.913 – 0.995)	**.028**	0.956 (0.920 – 0.993)	**.019**
SF36-RP	0.976 (0.953 – 0.999)	**.040**	0.987 (0.970 – 1.004)	.139
SF36-RE	0.978 (0.958 – 0.998)	**.034**	0.983 (0.967 – 0.999)	**.046**
SF36-VT	0.958 (0.915 – 1.003)	.064	0.940 (0.892 – 0.990)	**.019**
SF36-MH	0.955 (0.897 – 1.015)	.140	0.955 (0.897 – 1.017)	.154
SF36-SF	0.967 (0.933 – 1.003)	.076	0.969 (0.937 – 1.003)	.076
SF36-BP	0.968 (0.928 – 1.011)	.141	0.980 (0.947 – 1.014)	.245
SF36-GH	0.929 (0.875 – 0.987)	**.016**	0.969 (0.932 – 1.008)	.120
SLEDAI score	0.971 (0.891 – 1.057)	.490	1.040 (0.954 – 1.133)	.379
SLEDAI High/Very high (vs mild/moderate)	0.138 (0.015 – 1.302)	.084	1.818 (0.357 – 9.272)	.472
Sjogren's Syndrome (vs control)	3.545 (1.331 – 9.444)	**.011**	2.771 (1.053 – 7.290)	**.039**
Age (years)	0.986 (0.905 – 1.074)	.744	1.005 (0.922 – 1.095)	.910
Disease duration (years)	1.219 (0.958 – 1.550)	.107	1.113 (0.931 – 1.331)	.240
CRP	1.127 (0.901 – 1.410)	.296	1.189 (0.930 – 1.518)	.167
ESH	0.984 (0.942 – 1.028)	.477	0.993 (0.951 – 1.037)	.761
FSS	1.373 (0.876 – 2.151)	.167	2.219 (1.139 – 4.322)	**.019**
SF36-PF	0.980 (0.955 – 1.007)	.139	0.959 (0.928 – 0.990)	**.011**
SF36-RP	0.990 (0.974 – 1.005)	.186	0.982 (0.965 – 0.998)	**.028**
SF36-RE	0.990 (0.975 – 1.005)	.177	0.981 (0.965 – 0.997)	**.018**
SF36-VT	0.937 (0.882 – 0.996)	**.035**	0.959 (0.911 – 1.010)	.113
SF36-MH	0.782 (0.636 – 0.960)	**.019**	0.951 (0.901 – 1.003)	.063
SF36-SF	0.960 (0.927 – 0.995)	**.024**	0.927 (0.880 – 0.977)	**.005**
SF36-BP	0.984 (0.955 – 1.014)	.297	0.971 (0.941 – 1.003)	.078
SF36-GH	0.921 (0.862 – 0.984)	**.015**	0.903 (0.836 – 0.975)	**.009**
ESSDAI score	1.009 (0.841 – 1.210)	.926	1.168 (0.951 – 1.434)	.138
ESSDAI moderate/high (vs low)	0.583 (0.137 – 2.481)	.466	3.960 (0.865 – 18.119)	.076
Systemic Sclerosis (vs control)	2.364 (0.878 – 6.365)	.089	1.357 (0.492 – 3.746)	.556
Age (years)	1.042 (0.978 – 1.109)	.201	1.027 (0.963 – 1.096)	.418
Disease duration (years)	1.089 (0.929 – 1.276)	.293	1.119 (0.943 – 1.328)	.196
CRP	1.051 (0.858 – 1.288)	.629	1.051 (0.851 – 1.299)	.644
ESH	1.015 (0.967 – 1.066)	.537	0.976 (0.921 – 1.035)	.419
FSS	1.371 (0.824 – 2.283)	.224	2.499 (1.118 – 5.587)	**.026**
SF36-PF	0.980 (0.951 – 1.009)	.176	0.942 (0.900 – 0.987)	**.012**
SF36-RP	0.989 (0.970 – 1.007)	.228	0.971 (0.944 – 0.998)	**.035**
SF36-RE	1.004 (0.988 – 1.020)	.664	0.986 (0.969 – 1.004)	.133
SF36-VT	0.962 (0.925 – 0.999)	**.048**	0.945 (0.901 – 0.992)	**.021**
SF36-MH	0.938 (0.888 – 0.991)	**.023**	0.927 (0.871 – 0.988)	**.019**
SF36-SF	0.960 (0.928 – 0.993)	**.019**	0.953 (0.917 – 0.991)	**.016**
SF36-BP	0.973 (0.939 – 1.008)	.131	0.953 (0.911 – 0.997)	**.035**
SF36-GH	0.960 (0.921 – 1.002)	.059	0.941 (0.891 – 0.994)	**.030**
lcSSc (vs dcSSc)	0.058 (0.006 – 0.552)	**.013**	0.114 (0.012 – 1.076)	.114
Pulmoner involvement absent (vs present)	0.267 (0.054 – 1.326)	.201≠	0.033 (0.002 – 0.646)	**.003**≠≠

≠ calculated using Yates continuity correction. ≠≠ calculated using Fisher's exact test. Bold values indicated that statistically significance (p<.05).Abbreviations: FSS: Fatigue severity scale, HADS anxiety and HADS depression: Hospital anxiety and depression scale, DAS28-CRP: Disease activity score that uses c-reactive protein, DAS28-ERP: Disease activity score that uses erythrocyte sedimentation rate, ESSDAI: European league against rheumatism SS disease activity index, SLEDAI: Systemic lupus erythematosus disease activity index, dcSSc: Diffuse cutaneous scleroderma, lcSSc: Limited cutaneous scleroderma

4. DISCUSSION

This study evaluated fatigue, anxiety and/or depression in all CTD with details. Fatigue anxiety and/or depression were more common in patients with CTD. Patients who were at higher risk for anxiety and / or depression had more fatigue severity and lower QoL.

In all CTD such as RA, SS, SLE, and SSc, high rates of depression have been established (1). The etiopathology of depression in RA is quite complex. It has been suggested that an uncertain and variable prognosis of the disease leads to dysfunction, intensive pain, and social isolation caused by the disease, which may set the stage for both anxiety and depression. A decrease in drug compliance attributed to impaired quality of life and social withdrawal has also been reported. In a study by Van Korff et al., a strong relationship was found between RA disease activity and depression. Although it has been reported in some studies that there is an association between the severity of arthritis and depression, a direct relation between disease activation markers and severity of depression could not be demonstrated (8-10). In the present study, a statistically significant relation was found between disease activity and depression and anxiety. Even though anxiety and depression are usually coexisting disorders, anxiety has not drawn as much attention as depression in RA. It has been stated by El-Miedany et al. (11) that anxiety is as common as depression in RA patients. Investigators have established that the rate of depression is 66.2% and that of anxiety is 70%. However, in these studies, depression and anxiety levels in patients were not compared with those in non-patients (12).

Depression was found to be associated with high levels of fatigue. Although the etiology of fatigue is not known in RA, it is thought that it is multifactorial, including pain, disability, inflammation, sleep disorders, and psychosocial factors. Especially, increased production of IL-6 was stated to be associated with fatigue, which is one of the main components contributing to RA-related disability and morbidity. Although there are variable results in the studies on the relation of fatigue with disease activity, it has mainly been shown to be related to disease activity and in some studies, it has been proposed that fatigue be considered a sign of disease activity. In patients with high levels of inflammatory markers, lower HRQoL, higher levels of pain and fatigue are observed. The study of Gök K et al. revealed that levels of fatigue which were assessed by VAS, SF-36-vitality, FSS, and MAF, were quite similar between patients with RA and SSc. Levels of fatigue, measured by different scales, were significantly correlated with physical functions and HRQoL measures and psychometric variables in both groups (13). In the present study, consistent with the literature, fatigue scores have been high and associated with disease activity and low HRQoL. In SLE, depression is a multi-factor condition caused by the interaction between behavioral and biological pathways. Previous studies have reported that anxiety disorders occur twice as commonly in SLE patients as controls. In individual studies, depression prevalence has been estimated to vary between 2% and 91.7% (14, 15). It has been stated that the severity of depression has a positive correlation with increased disease activity, which may reflect significant CNS damage in SLE (16). In another study, the prevalence of depression was found to be 16 %, without any relation with disease activity and organ damage, and it was established that merely 7% of patients were on antidepressant treatment (17). In the present study, no relation was found between disease activation and depression and anxiety, which may be explained by the lack of patients with CNS clinical involvement and few cases. Depression is associated with an increase in pro-inflammatory cytokines, and increased cardiovascular risk may be associated with the accumulated inflammatory burden. Therefore, improvement of depression management in SLE patients may directly or indirectly affect psychological health and physical health, including cardiovascular disease risk (16, 17).

Fatigue is a symptom that occurs in 80% of SLE patients and markedly reduces the quality of life (18, 19). Consistent with the literature, in the present study, fatigue was associated with depression and anxiety. The relation between fatigue and organ damage and disease activity varies between studies. Wysenbeek et al. observed arthritis more commonly in SLE patients with fatigue than those without fatigue. Similarly, Krupp et al. found a strong association between fatigue and clinicians' opinion regarding disease activity. However, no relation could be demonstrated between fatigue and disease activity in three studies, similar to the present study (18-21).

Fatigue, pain, and depression are factors that exert adverse effects on HRQoL. In the study of Mok et al., in comparing SLE patients in long-term remission with those in short-term remission, better HRQoL and MH were observed in the former in all SF36 components except PF. Besides, in the study of Tench et al., it was observed that although fatigued has a correlation with sleep quality, anxiety, depression, and all components of SF-36, even in early and mild periods of the disease, fatigue exerts a markedly adverse effect on morbidity (22, 23). Compatible with the literature, it was established that patients had higher levels of fatigue, depression, and anxiety and generally lower levels of HRQoL compared to healthy controls.

SS may also have some extra glandular features such as pain, fatigue, anxiety, and depression, which have the potential of impairing HRQoL and exert a negative impact on psychological, physical, and social functioning. The prevalence of depression was established to be high, and estimations range from 8.33% to 75.5 %. The exact etiopathogenesis of depression in SS remains uncertain (24). In SS, a relation has been observed between pain, depression, fatigue, and pro-inflammatory cytokines. It has been reported that the prevalence of fatigue is around 70 % among SS patients. In SS patients, psychological distress and constant fatigue were correlated with low HRQoL, loss of work productivity, increasing levels of disability, and medical costs. Therefore, depression and anxiety may be suitable targets for interventions to improve subjective health and

quality of life (25-28). In the present study, consistent with the literature, high rates of fatigue, anxiety, and depression and low levels of HRQoL were observed, but they were not found to be associated with disease activity. Despite the effect of fatigue enhancing depression, it was found to be effective in anxiety.

SSc patients report high levels of pain, fatigue, and physical dysfunction. In addition to physical impairment and symptoms, SSc patients have been stated to have higher rates of depression and anxiety (18%-65%) compared to the general population and other patient groups, and a significant correlation has been reported between depression and anxiety. In the present study, it was observed that the risk of depression and anxiety did not increase in SSc patients compared to controls, which is discrepant with the findings of previous studies. This difference may be explained by our small patient group and the divergence between measurement parameters used. In some studies, depressive symptoms, fatigue, and other physical symptoms were related to SSc severity (28, 29). Fatigue occurred more commonly in patients with pulmonary symptoms. In the present study, fatigue was observed to increase the risk of depression. In the study of Legendre et al., it was stated that in patients with SSc, depressive symptoms were associated with pulmonary involvement but not with skin involvement, organ involvement, and disability. In the study of Beretta et al. on SSc patients, depressive symptoms were found to be associated with diffuse skin involvement, pulmonary involvement, generalized pain, Reynaud phenomenon, severe disease, and digital ulcer. In many studies in patients diagnosed with SSc, diffuse skin involvement and visceral organ involvement were found to be associated with depressive symptoms.

Similarly, Danieli et al. established that in patients with diffuse skin involvement, quality of life was impaired at a higher degree. The study of Muller et al. stressed that quality of life and female sex are independent risk factors for depressive symptoms. Functional disability and anxiety were found to be associated with low HRQoL (30, 31). In keeping with previous studies, depression and anxiety were associated with functional status and quality of life in the present study. The present study may be considered significant in that it is a comprehensive study on depression, anxiety, fatigue, and HRQol in CTD patients. However, as it is a cross-sectional study, it is not possible to reach any definitive conclusion on the relation between disease activity and psychiatric impairment. Prospective studies with larger patient series may shed light on factors that effect the development of depression and anxiety in CTD patients.

Some limitations in our study should be addressed. The present study was performed at a single tertiary care center. Moreover, the research included a relatively small number of patients. The strengths of this study include our assessment of fatigue and psychological morbidity with a valid and trustworthy tool such as FSS and HADS, as well as extensively investigated laboratory and clinical markers.

5. CONCLUSION

It is obvious that irrespective of the causality relation, psychiatric morbidities and fatigue may be present in CTD patients. Early diagnosis and judicious intervention are essential in order that the adverse effect of anxiety and depression on quality of life and disease outcomes can be reduced to the minimum.

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