

Extraarticular manifestations in Turkish patients with rheumatoid arthritis: impact of EAMs on the health-related quality of life in terms of disease activity, functional status, severity of pain, and social and emotional functioning

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Abstract The aim of our study was to investigate extra-articular manifestations (EAMs) in Turkish patients with rheumatoid arthritis (RA) and also assess the impact of EAMs on various health-related quality of life (HRQoL) domains, including physical, social, emotional, mental functioning, and bodily pain. A total of 150 patients were included in the study. EAMs were identified clinically. Pulmonary involvement was confirmed by using pulmonary function tests (PFT) and high-resolution computed tomography (HRCT), atlantoaxial subluxation by cervical spine X-rays. Peripheral neuropathy, rheumatoid nodules, and Sicca symptoms were picked up on clinical examination. Peripheral neuropathy was also confirmed by electroneurophysiologic studies. Patients were evaluated by Rheumatoid Arthritis Quality of Life (RAQoL), and Short form-36 (SF36). The quadrivariate Disease Activity Score-28 (DAS28) was used for measuring disease activity. Functional status was evaluated by using the Stanford Health Assessment Questionnaire (HAQ). The severity of pain was documented by using 10-cm Visual Analog Scale-Pain (VAS-pain). EAMs were observed in 50 patients (33.3%). These were pulmonary involvement (28.7%), rheumatoid nodules (14.7%), Sicca Syndrome (8%), peripheral neuropathy (2.7%), and atlantoaxial subluxation (0.7%), respectively. It was not recorded any statistically significant difference in HAQ, DAS28, VAS-pain, and RAQoL scores between the patient groups with and without EAMs. Patients with EAMs scored significantly lower in physical functioning, role-physical, and role-emotional

subgroups of SF36 ($P < 0.01$). Presence of EAMs is not directly associated with disease activity and functional status, but influences negatively HRQoL including physical and emotional functioning.

Keywords Rheumatoid arthritis · RA · Health-related quality of life · HRQoL · RAQoL · Extraarticular manifestations · EAMs

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, and also a multisystem disease associated with a range of extraarticular manifestations (EAMs). Patients experience high levels of pain, functional disability, decreased ability to work, and premature mortality [1]. RA, its treatments, and EAMs arising from both result in detrimental effects on health-related quality of life (HRQoL), including physical, psychological, and social functioning. Presence of EAMs is associated with more severe disease and increased mortality [2].

RA has a significant impact on HRQoL. Generic and disease-specific HRQoL instruments may have greater ability to measure functional impairments resulting from the specific disease and detect smaller changes in health, relative to generic instruments. Generic instruments are used in the general population to compare results between disease groups and evaluate broad variety of disease-related factors [2, 3].

The present study aimed to investigate EAMs in RA patients in Turkey and assess the impact of EAMs on various HRQoL domains in terms of disease activity, functional status, severity of pain, and social and emotional functioning.

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Patients and methods

A total of 150 RA patients were included in the study. All of the patients gave their informed consent prior to their inclusion in the study. All of them had a positive diagnosis of RA according to the 1987 American College of Rheumatology (ACR) diagnostic criteria [4]. The demographic data (age, gender), disease properties [disease duration, rheumatoid factor (RF) seropositivity], and drug use were recorded. EAMs were identified clinically. Pulmonary involvement was defined as pleuritis, interstitial disease, and pulmonary nodules confirmed by using pulmonary function tests (PFT) and high-resolution computed tomography (HRCT). Atlantoaxial subluxation was confirmed by cervical spine X-rays. Peripheral neuropathy, rheumatoid nodules, and Sicca symptoms were picked up on clinical examination. Peripheral neuropathy was considered compression neuropathy and peripheral neuropathy confirmed by electroneurophysiologic studies. Number of swollen and tender joints and erythrocyte sedimentation rate (ESR) were evaluated. The quadrivariate Disease Activity Score-28 (DAS28) was used for measuring disease activity [5]. The severity of pain was documented by using 10-cm Visual Analog Scale-Pain (VAS-pain) [6]. HRQoL was evaluated by using one generic [Short form-36 (SF36)] [7] and one disease-specific [Rheumatoid Arthritis Quality of Life (RAQoL)] [8] HRQoL scales. The Stanford Health Assessment Questionnaire (HAQ) was used for evaluation of the functional status [9].

Statistical analyses

Data were presented by descriptive analysis with means \pm standard deviation (SD). Differences between patients with and without EAMs were assessed using independent samples *T*-test. A value of $P < 0.05$ was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences-13.0 (SPSS-13.0) software.

Results

Demographic characteristics

A total of 150 RA patients, 126 women and 24 men, were included in the study. Female–male ratio was 5.3. Mean age of the patients was 53.2 ± 12.1 (24–79) years. Mean age was 52.9 ± 12.2 years for women and 55.2 ± 11 years for men.

Clinical findings and disease activity

The mean disease duration of the patients was 147.3 ± 99.4 months. The mean ESR was 21.9 ± 16.1

(2–80) mm/h. RF was positive in 132 patients (78.7%). Mean numbers of swollen and tender joints were 0.7 ± 1.5 and 3 ± 4.7 , respectively. Mean DAS28 score was 3.4 ± 1.3 (median: 3.1); 50 patients (33.3%) were in remission (DAS28 score = <2.6), 30 patients (20%) had mild disease activity (DAS28 score: 2.6–3.2), 51 patients (34%) had moderate disease activity (DAS28 score: 3.2–5.1), and 19 patients (12.7%) had severe disease activity (DAS28 score ≥ 5.1).

Functional status and quality of life

Mean score was 0.8 ± 0.8 for HAQ and 11.8 ± 9.7 for RAQoL. The mean \pm SD HRQoL scores of the patients were 67.5 ± 26.6 , 62.5 ± 48.4 , 62.1 ± 25.3 , 49.9 ± 26 , 58.8 ± 21.5 , 72.7 ± 22.8 , 67.8 ± 46.2 , and 62.5 ± 14.4 in the physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health subgroups of SF-36, respectively. Demographics and clinical data are summarized in Table 1.

Table 1 Demographic and clinical patient data

	Minimum	Maximum	Mean	SD	Median
Age	24	79	53.3	12.1	54
Number of swollen joints	0	10	0.7	1.5	0
Number of tender joints	0	26	3	4.7	1
ESR (mm/h)	2	80	21.9	16.1	18
Disease duration (month)	2	480	147.3	99.4	120
DAS28	0.5	7.6	3.4	1.3	3.1
HAQ	0	3	0.8	0.8	0.75
Pain (VAS, 10 cm)	0	10	4.2	2.7	4
RAQoL	0	30	11.8	9.7	11
SF36 physical functioning	0	100	67.5	26.6	70
SF36 role-physical	0	100	62.5	48.4	100
SF36 bodily pain	0	100	62.1	25.3	62
SF36 general health	0	100	49.9	26.0	61
SF36 vitality	0	100	58.8	21.5	65
SF36 social functioning	13	100	72.7	22.8	88
SF36 role-emotional	0	100	67.8	46.2	100
SF36 mental health	32	84	62.5	14.4	64

ESR Erythrocyte sedimentation rate, DAS28 Disease activity score, HAQ (Health Assessment Questionnaire): functional status health assessment Questionnaire, VAS Visual Analog Scale, RAQoL (Rheumatoid arthritis quality of life): rheumatoid arthritis quality of life scale, SF36 Short form-36

Extraarticular manifestations

EAMs were noted in 50 patients (33.3%). The most common was pulmonary involvement, which was identified in 43 patients (28.7%). HRCT was abnormal in 28.7% of the patients. Most frequent HRCT findings were pleuritis, pulmonary nodules, interstitial disease, ground glass attenuation, and honeycombing. Pulmonary involvement was followed by rheumatoid nodules (22 patients, 14.7%), Sicca Syndrome (12 patients, 8%), peripheral neuropathy (4 patients, 2.7%), and atlantoaxial subluxation (1 patient, 0.7%), respectively (Table 2).

Medications

One or more disease-modifying antirheumatic drugs [DMARD (Methotrexate, leflunamide, sulphasalazine, and antimalarials)] or anti-TNF agent (infliximab, etanercept, adalimumab) were currently being used by 146 (97.3%) patients. Of all the patients, 91.3% (137 patients) were under DMARD therapy, and 12% (18 patients) were under anti-TNF therapy. Methotrexate (MTX) was the most commonly prescribed DMARD. And 73.3% of the patients (110 patients) were under MTX therapy. The ratio of the patients receiving MTX monotherapy was 49.3% (74 patients). Current medication of the patients is shown in Table 3.

Table 2 Frequency of extraarticular manifestations in 150 RA patients (n = 50)

EAMs	Number (%)
Overall EAMs	50 (33.3)
Pulmonary involvement	43 (28.7)
Rheumatoid nodules	22 (14.7)
Sicca syndrome	12 (8)
Peripheral neuropathy	4 (2.7)
Atlantoaxial subluxation	1 (0.7)

Table 3 Drug use in 150 RA patients (n = 50)

	Number	Percentage
Methotrexate	110	73.3
Sulphasalazine	19	12.7
Leflunomide	18	12
Antimalarials	28	18.7
Infliximab	2	1.3
Etanercept	12	8
Adalimumab	4	2.7
Azathiopurin	1	0.7
Corticosteroids	82	54.7

It was not recorded any statistically significant difference in HAQ, DAS28, VAS-pain, and RAQoL scores between the patient groups with and without EAMs (Table 4).

Patients with EAMs scored significantly lower in the physical functioning, role-physical, and role-emotional subgroups of SF36 (P < 0.01). It was not found any statistically significant difference in the bodily pain, general health, vitality, social functioning, and mental health subgroups of SF36 between patient groups with and without EAMs (Table 5).

Discussion and conclusion

In the present study, EAMs were seen in 50 patients (33.3%). These were pulmonary involvement (28.7%), rheumatoid nodules (14.7%), Sicca Syndrome (8%), peripheral neuropathy (2.7%), and atlantoaxial subluxation (0.7%), respectively. The frequency of EAMs in Turkish RA patients was reported as 22.4% in the study of Bodur

Table 4 The relation between presence of EAMs and clinic and radiological parameters

EAMs	HAQ	DAS28	VAS-pain	RAQoL
Present (n = 50)	1.3 ± 0.7	4.1 ± 1.4	6.1 ± 2.6	18 ± 9.1
Absent (n = 100)	0.6 ± 0.7	2.9 ± 1.2	3.3 ± 2.2	8.6 ± 8.6
P value*	0.52	0.07	0.198	0.337

EAMs Extraarticular manifestations, *HAQ* (Health Assessment Questionnaire): functional status health assessment questionnaire, *DAS28* Disease activity score, *VAS* Visual analog scale, *RAQoL* (Rheumatoid Arthritis Quality of Life): rheumatoid arthritis quality of life scale

* P < 0.05 (significant)

Table 5 The relation between presence of EAMs and SF36 subgroups

	EAMs		P value
	Present (n = 50)	Absent (n = 100)	
SF36 physical functioning	47.8 ± 27.4	76.5 ± 20.8	0.001**
SF36 role-physical	40 ± 49.5	74.5 ± 43.1	0.001**
SF36 bodily pain	47.9 ± 22.9	68.9 ± 23.1	0.57
SF36 general health	34.1 ± 25.1	57.8 ± 23.3	0.18
SF36 vitality	45.2 ± 18.8	64.9 ± 20.5	0.36
SF36 social functioning	58.2 ± 23.6	78.8 ± 20.3	0.09
SF36 role-emotional	43.3 ± 49.6	76.9 ± 41.5	0.001**
SF36 mental health	56.3 ± 13.3	65.2 ± 12.9	0.52

EAMs Extraarticular manifestations, *SF36* Short form-36

* P < 0.05 (significant); ** P < 0.01 (highly significant)

et al. They included ophthalmic involvement (8.7%), pulmonary involvement (8%), subcutaneous nodules (7.5%), and neurological involvement (1.9%) [10]. Calguneri et al. reported the rate of EAMs in RA patients in Turkey as 38.4%. Rheumatoid nodules (18.1%) were the most common. Sicca syndrome and pulmonary findings were present in 11.4%, 4.8% of the patients, respectively [11]. In the study of Cimmino et al., a total of 587 Italian patients with RA were included, and EAMs were present in 240 patients (40.9%). The most common EAMs were Sicca syndrome (17.5%) and rheumatoid nodules (16.7%). Pulmonary involvement was seen in 6.3% [12]. Carmona et al. found the rate of EAMs in Spanish patients as 36.2%: rheumatoid nodules 24.5%, Sjogren's Syndrome 17%, and interstitial lung disease 3.7% [13].

Prevalences of overall EAMs, rheumatoid nodules, and Sicca syndrome in Turkish RA patients were reported quite similar to ones of Mediterranean populations in previous studies. Apart from that, pulmonary involvement was more frequent in our series. There may be three reasons for more frequent pulmonary involvement. The first one is the sensitive diagnostic radiological methods that were used. Also, Demir et al. assessed pulmonary involvement using HRCT in asymptomatic nonsmoking Turkish RA patients. PFT was abnormal in 23.5%, and HRCT was abnormal in 68%. They noted that the incidence of pulmonary abnormalities in asymptomatic RA patients might be higher than previously reported by using a highly sensitive technique such as HRCT [14]. The second one is patient selection criteria. Our group of patients was composed of mostly severe ones requiring regular controls in a tertiary hospital. Having more frequent and also high-dosage medicine may result in medicine toxicity (such as rheumatoid nodulosis and MTX-induced pneumonitis) as the last reason.

In another Mediterranean country, Greece, prevalence of EAMs was reported as 43.2%: Sicca syndrome 24%, lung fibrosis 5%, and rheumatoid nodules 4.5%. However, rheumatoid nodules are less frequent than other Mediterranean countries [15].

The present study investigated the impact of EAMs on HRQoL including physical, social, emotional, mental functions, and pain. The relationship between the presence of EAMs and disease activity, functional status, pain, radiological damage was evaluated. Patients with EAMs scored significantly lower in the physical functioning, role-physical, and role-emotional subgroups of SF36. This is concordant to the other studies in the literature. Bedi et al. investigated HRQoL in 81 patients with RA. HRQoL was estimated by the WHOQoL-Bref. Patients with EAMs had lower World Health Organization quality of life instrument (WHOQoL-Bref) scores (statistically significant for physical subgroup) compared to patients without EAMs [16]. Also in the study of Haroon et al., RA patients with EAMs

scored significantly lower in the physical health domain of WHOQoL [17]. Similarly Al-Ghamdi et al. suggested that EAMs led to a worse quality of life in RA patients [18].

In conclusion, extraarticular manifestations of RA are common and are associated with more active and severe RA. In our study, it's concluded that the presence of EAMs is not directly associated with disease activity and functional status, but has a negative influence on HRQoL including physical and emotional functioning. To prevent developing of EAMs with early diagnosis and also more aggressive drug therapies may result in an increase in HRQoL.

Conflict of interest None.

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