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Impact of sustained remission on quality of life among women with rheumatoid arthritis and systemic lupus erythematosus: a prospective observational study

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Abstract

Background: Health-related quality of life (HRQOL) as a patient reported outcome plays important roles in the life of patients with RA (rheumatoid arthritis) and SLE (Systemic lupus erythematosus) as well as their families. Evaluating the impact of sustained remission on HRQOL is important and could be of potential help in daily practice. Thus, we aimed to assess and compare prospectively the impact of sustained remission on HRQOL in Saudi RA and SLE female cohorts.

Results: Sixty-two female patients with active RA and 34 female patients with active SLE fulfilled the inclusion-, entry- and follow-up criteria. At baseline, the SLE patients had significantly better SF-36 scores than the RA patients. In both groups, significant correlations were found between disease activity and physical (PCS) and mental (MCS) components summary of the SF-36 (all p 's ≤ 0.001). In sustained remission, both SLE and RA patients showed significant improvements of the SF-36 scores ($p < 0.001$) compared to baseline. RA patients in sustained remission had a significantly better general health, bodily pain and physical functioning, and total PCS scores ($p < 0.001$) than those with SLE.

Conclusions: Both SLE and RA patients in sustained remission showed strongly improved HRQOL. In sustained remission, RA patients had comparable or better HRQOL than SLE patients.

Keywords: Remission, Quality of life, Rheumatoid arthritis, Systemic lupus erythematosus, Disease activity

Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that may lead to joint inflammation, deformities, and organ involvement [1]. Physical deformities, painful disabilities, and impairment may all contribute to depression in people with RA [2]. Depression is estimated to be five times more common in

people with RA than in the general population [3]. The combination of RA and depression has been shown in a number of studies to increase impairment and lower quality of life [4–6]. Also, in the early stages of the disease, RA patients were found to have lower levels of health-related quality of life (HRQOL) than the general population [6].

Systemic lupus erythematosus (SLE) is a systemic autoimmune rheumatic disease affecting 1–12 people per 5000 worldwide [7]. Depressive conditions are prevalent in 17–75 percent of SLE patients, according to studies [8, 9]. Depression was found to be more common in SLE patients than in the general population [10] and was

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found to be a significant indicator of poor HRQOL in those patients [11].

Studies have found a connection between RA patients' disease behavior and the presence of depression, as well as a reduction in HRQOL [4, 5, 12–14]. The same was found in SLE patients, who had stronger HRQOL when they had a longer clinical recovery and less disease activity [9, 12, 15–17]. Although the impact of disease activity on HRQOL has been studied in the past, the impact of disease remission, particularly sustained remission, has yet to be investigated in Arab patients. In addition, little is known about the effects of remission in RA versus SLE. Just one prospective study in Mexican RA and SLE patients was identified in a thorough literature review, comparing the impact of disease remission, in particular of sustained remission, has hardly been studied yet in Arab patients. Also, very little is known about the differential impact of remission in RA and SLE. A careful literature search found only one prospective study in Mexican RA and SLE patients, comparing the effect of remission on HRQOL of both RA and SLE patients [18].

Recently, the remission criteria of RA and SLE patients have been clearly defined [18, 19]. As HRQOL plays an important role in the lives of patients with RA and SLE as well as their families, evaluating the impact of sustained remission on HRQOL is important and could be of potential help in daily practice. It is expected that prolonged remission will improve QOL in both RA and SLE. But it is necessary to gather real life data and confirm our beliefs.

As these data are lacking in Arab populations, we decided to assess and compare the impact of sustained remission on HRQOL in two cohorts of Saudi RA and SLE female patients.

Methods

Study design

This study was a prospective comparative observational study among RA and SLE patients. Adult female Saudi RA patients > 18 years who fulfilled the 2010 RA classification criteria [19] with active 28-joint disease activity score (DAS28 > 3.2) [20] and adult female Saudi SLE patients who fulfilled the American College of Rheumatology (ACR) classification criteria [21] with active Systemic Lupus Disease Activity Index scores (SLEDAI > 4) [22] visiting the outpatient rheumatology clinics of the Al Hada Armed Forces Hospital, Taif, Saudi Arabia, were invited consecutively by a rheumatologist from January to June 2016 (6 months) to participate in the study.

All patients underwent full clinical and laboratory assessment. The DAS28-ESR [20] was measured by rheumatologists in the RA patients at baseline of the study and every 3 months during 2 years follow-up. The

SLEDAI [22, 23] was measured by rheumatologists in the SLE patients at baseline of the study and every 3 months during 2 years follow-up. Patient-reported HRQOL was assessed with the SF-36 health survey at baseline and in patients after sustained remission [6, 11]. The primary outcomes were HRQOL in RA and SLE patients in sustained remission compared with baseline data.

Inclusion criteria

Only patients achieving sustained remission that persisted for at least 2 consecutive clinic visits over 8 months were included. RA remission was defined when DAS28 \leq 2.6 and SLE remission with clinical SLEDAI-2K of 0 and a physician global assessment \leq 2.

Exclusion criteria

Patients with active neuropsychiatric lupus, other autoimmune disease, and chronic comorbidities such as thyroid disorder, diabetes, hypertension, heart failure, and stroke were excluded. Patients known to have psychiatric related illness were also excluded at initial study screening.

Definitions of remission

The SLE patients in remission were defined according to the Definition of Remission in SLE (DORIS) remission criteria with a clinical SLEDAI-2K of 0 and a physician global assessment \leq 2 and with excluding the items 'hypocomplementemia' and 'anti-dsDNA' [24]. During the sustained remission, the patients needed to be on stable treatment. In both groups, the treatment was allowed to include a maintenance dosage of anti-malarials and stable maintenance dose of immunosuppressive agents and/or biologic disease modifying anti-rheumatic drugs and stable dose of low-dose glucocorticoids \leq 5 mg prednisone daily. If recently a higher dosage of glucocorticoids and/or immunosuppressive drugs were used to treat increased disease activity a patient was not considered in remission.

RA remission was defined when DAS28 \leq 2.6. According to Smolen et al. [25] RA treat to target sustained remission was defined as achieving remission or low disease activity continuously maintained for a minimum of 6 months. However, the duration to consider sustained remission in SLE has not yet been clearly defined in literature. Therefore, the recommendation to have at least 6 months remission or low disease activity prior to getting pregnant [26] can also be considered sustained remission for SLE. In the current work, we defined sustained remission by achieving first remission in RA or SLE, then to maintain such status for at least 8 months or more as sustained remission during at least 2 rheumatology clinic follow-up visits.

Laboratory assessments

All patients were followed in the rheumatology clinic every 3 months, with clinical and laboratory assessments during each visit to evaluate the disease activity and confirm remission status. In all patients, the erythrocyte sedimentation rate (ESR) by Westergren method and complete blood count (CBC) was taken. For RA patients, anti-cyclic citrullinated peptide antibodies (anti-CCP Abs) and rheumatoid factor (RF) were assessed using the chemiluminescence microparticle immunoassay (CMIA), Abbott, USA. For SLE patients, anti-nuclear antibodies (ANA) were assessed by the indirect immunofluorescence using Kallestad kit, Aesku System, Germany; C3, C4, serum creatinine, and anti-double stranded DNA by the indirect immunofluorescence technique. Urine analysis was done chemically and microscopically with protein creatinine ratio, urine casts.

Health-related quality of life

Information about HRQOL was obtained using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [27], which is a widely used tool for assessing HRQOL in patients with various rheumatic conditions, including RA and SLE [6, 11]. The SF-36 contains 8 multi-item scales that assess the domains of: physical functioning (PF, 10 items), social functioning (SF, two items), role limitations due to physical health problems (RP, four items), role limitations due to emotional problems (RE, three items), mental health (MH,

five items), vitality (VT, four items), bodily pain (BP, two items), and general health perceptions (GH, five items). Transformed subscale scores range from 0 to 100, with 0 being the worst and 100 the best possible score.

The physical and mental components of the eight scales can be combined into two scales, the Physical Component Summary (PCS) and Mental Component Summary (MCS). Each of them aggregates four health domains. The PCS aggregates the PF, RP, BP, and GH domains, and the MCS aggregates the VT, SF, RE, and MH domains [28]. The validated Arabic version of the SF-36 was used. This version proved to be reliable in a previous study [29]. The SF-36 was filled in at baseline with active disease and after sustained remission.

We chose to measure function with SF-36 as this was a validated outcome measure in both RA and SLE, while the Health Assessment Questionnaire (HAQ) was only validated in RA patients.

Ethics

The study was approved by the local ethical research committee at Al Hada Armed Forces Hospital, KSA (Registration number H-02-T-078), and performed according to the 1964 Helsinki Declaration. All patients had provided written informed consent.

Statistical analysis

Data was analyzed using SPSS software version 22. Descriptive statistics were calculated as the mean ±

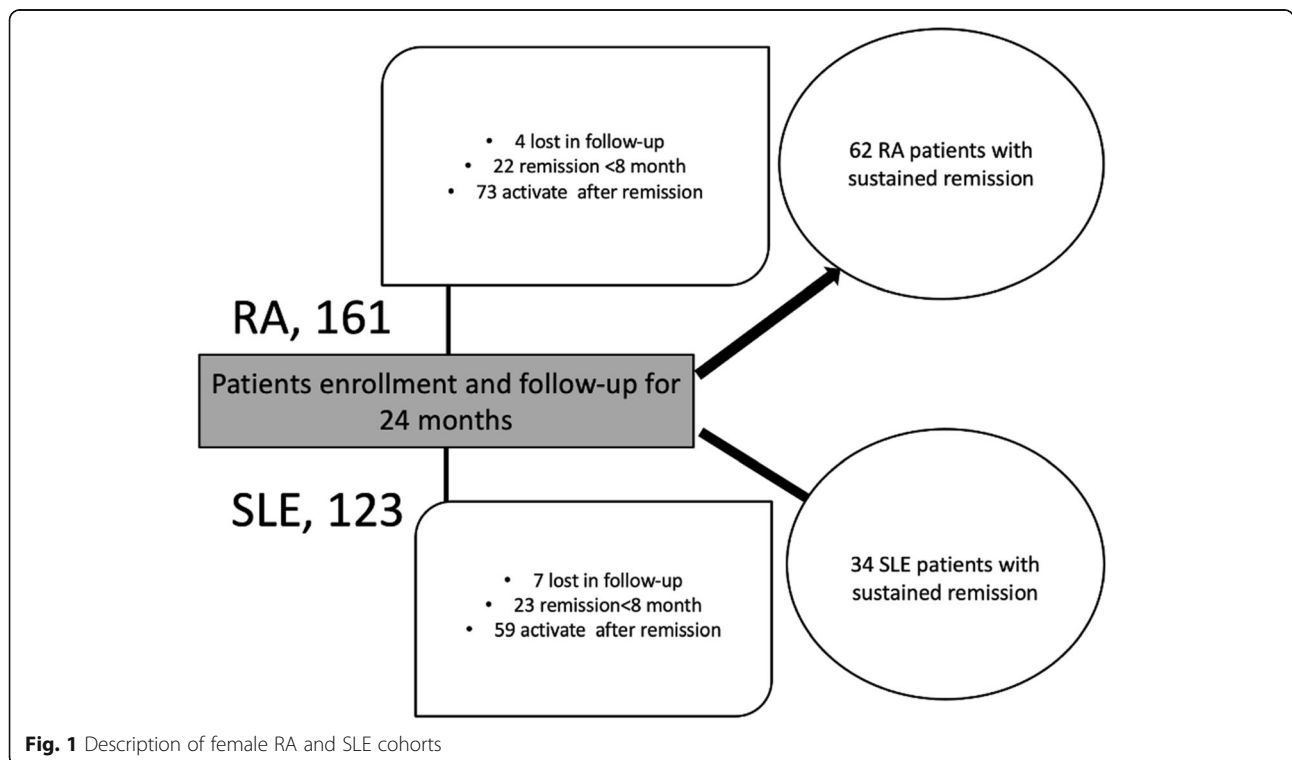


Fig. 1 Description of female RA and SLE cohorts

Table 1 Clinical and demographic data of the studied groups

	RA (N = 62) (Mean ± SD)	SLE (N = 34) (Mean ± SD)	P value
Age (years)	35.9 ± 6.	37.8 ± 6	$p > 0.05$
Disease duration (months)	15.3 ± 6.	17.1 ± 6.8	$p > 0.05$
ESR	51.8 ± 7.9	29.3 ± 15.3	$p < 0.001$
Duration to induce remission (months)	5.3 ± 1.7	7.1 ± 2.3	$p < 0.001$
DAS 28	5.3 ± 1	–	
SLEDAI		30.9 ± 6.1	

standard deviation (SD) for numerical data and frequency and percentages for categorical data. Paired *t* tests were applied to compare repeated measurements, and independent *t* tests were used to compare scores between independent samples. Pearson correlations between disease activity and SF-36 scores were calculated. Correlations were interpreted as very low when < 0.30 , low when $0.30–0.50$, moderate when $0.50–0.70$, high when $0.70–0.90$, and very high when > 0.90 [30]. Chi-squared tests (χ^2) of independence were applied to compare categorical data. Significance level was set at 5% for all analyses.

Results

During the initial screening, 161 patients with active RA, and 123 patients with active SLE were included. Rheumatological medications used at baseline to induce remission were 92 (57.2%) of the RA patients and 118 (94%) of the SLE patients were on DMARDs either monotherapy or in combination. Of the RA patients, 69 (42.8%) were treated with biologics (anti-TNF, Abatacept, Tocilizumab, Rituximab) either monotherapy or in combination with other DMARDs, and only 5 (4%) of SLE patients were treated with biologics (one patient received Rituximab and 4 patients were on Belimumab).

Patients achieving sustained remission

Only patients in sustained remission were included in the current study. During follow-up, sustained remission was achieved by 62 (38.5%) of the patients in the RA cohort and 34 (27.6%) of the patients in the SLE cohort (Fig. 1).

The demographic characters of the RA and SLE patients were shown in Table 1. The average time needed to induce remission in RA was 5.3 ± 1.7 and 7.1 ± 2.3 months in RA and SLE patients, respectively, with statistically significantly longer duration to induce remission in SLE ($p = < 0.001$). No significant differences were found between RA and SLE patients with respect to their age and disease duration at inclusion in months. The RA patients had a significant higher ESR (51.8 ± 7.9 vs 29.3 ± 15.3 , $p = < 0.001$) than the SLE cases (Table 1).

At baseline, significant correlations were found between disease activity and PCS and MCS scores (p values ≤ 0.001) in both RA and SLE groups. This correlation was strong and negative with PCS and MCS (r 's – 0.73 to – 0.80) in both groups (Table 2).

SLE patients had significantly better scores on all SF-36 subscales compared to RA patients during active disease. After achieving sustained remission status, the SF-36 scores had improved in both cohorts, where RA patients now scored significantly better when compared to SLE groups for three subscales (GH, BP, PF) and for the total PCS score (Fig. 2). The mean values of PCS and MSC components scores of the SF-36 of the RA and SLE cohorts showed highly significant improvements after remission ($p \leq 0.001$) (Table 3).

Discussion

SLE and RA are both autoimmune disorders that have a significant effect on physical and mental health [5, 13]. In active disease, the caregivers' psychological burden increases [31]. We aimed to assess the relation of disease activity with HRQOL, as well as the impact of sustained remission, which has hardly been studied in Arab patients.

The present prospective study revealed that 38.5% of the RA cohort could achieve sustained remission for 8 months or more, compared to 27.6% of the SLE cohort. Comparable figures were found by Pascual-Ramos et al. who found that 58% of RA patients achieved sustained remission compared to 30.6% of SLE patients [18]. This

Table 2 Correlation between disease activity in both female cohorts and physical and mental component summary scores of SF-36

Groups of patients	DAS28 RA (N = 62) r (p)	SLEDAI SLE (N = 34) r (p)
PCS	– 0.50 (< 0.001)	– 0.64 (< 0.001)
MCS	– 0.46 (< 0.001)	– 0.62 (< 0.001)

Abbreviations: SF-36 Study 36-Item Short-Form Health Survey, DAS28 Disease activity score, RA Rheumatoid arthritis, SLEDAI Systemic Lupus Disease Activity Index, SLE Systemic lupus erythematosus, PCS Physical components summary of the SF-36, MCS Mental components summary of the SF-36, ρ Spearman's rho

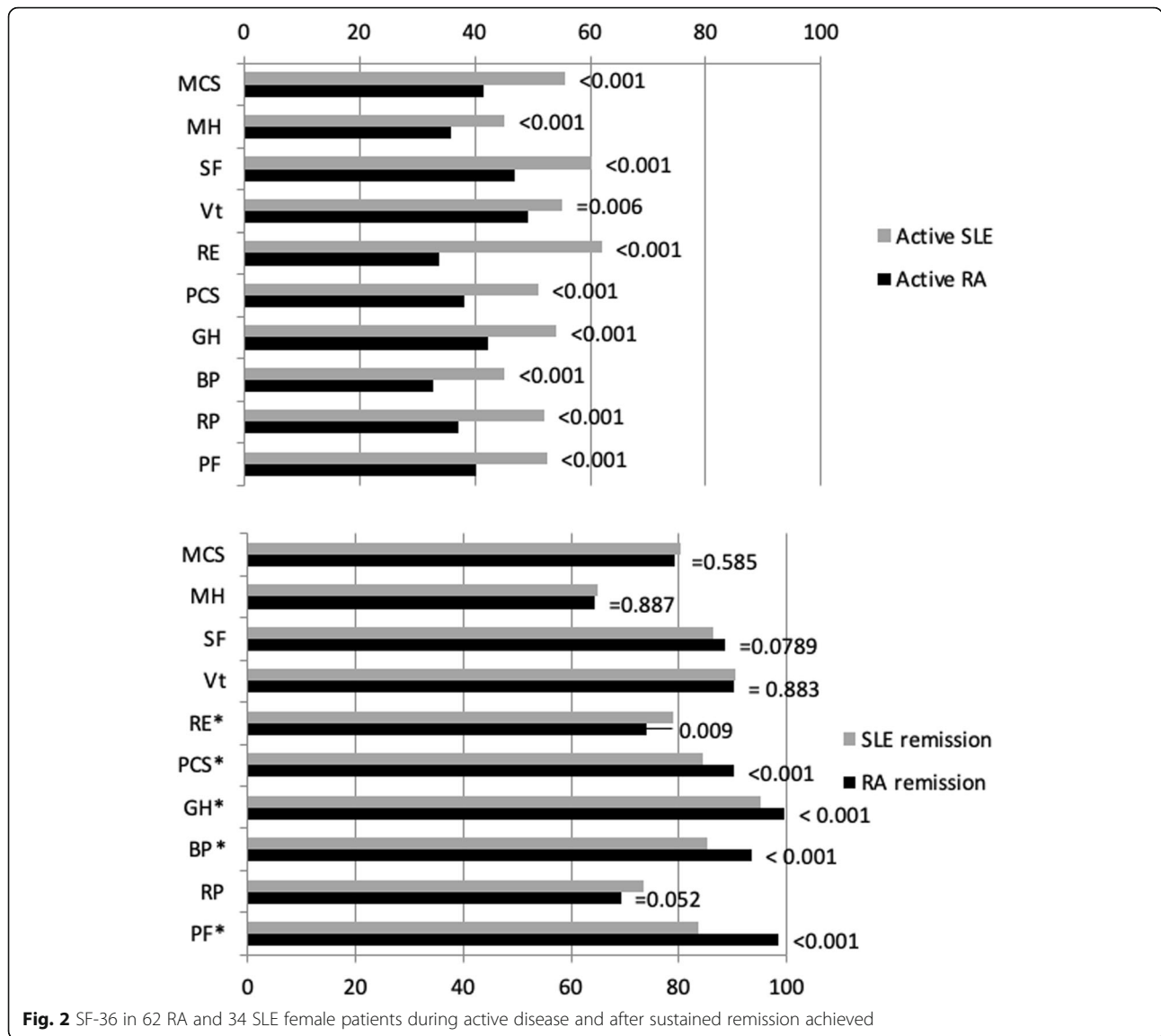


Fig. 2 SF-36 in 62 RA and 34 SLE female patients during active disease and after sustained remission achieved

difference was explained by the effect of new RA medications and treatment strategies [32]. The PCS portion of the SF-36 has been linked to SLE disease activity and organ damage in previous SLE studies [17, 33]. In the current research, SLE patients in sustained remission had a substantial increase in the MCS domain as compared to those with active disease. In comparison to this finding, Tsang-A-Sjoe et al. found that during the 2

years of the study, MCS scores did not vary between patients with active disease and those in remission in a longitudinal study of SLE patients [16]. A slightly higher percent of sustained remission among SLE patients was found in a recent retrospective study, where 42.2% of the 237 SLE patients achieved sustained remission [15].

HRQOL concerns the physical and functional health, and reflects a view of patients' social environment and

Table 3 Comparison between PCS and MSC components scores among female RA and SLE cohorts before and after remission

Parameter	RA (N = 62)				SLE (N = 34)			
	Before	After	t	p value	Before	After	t	p value
PCS	38.10 ± 5.66	90.27 ± 5.59	59.1	< 0.001	51.01 ± 10.9	84.43 ± 5.65	14.6	< 0.001
MSC	41.44 ± 2.92	79.33 ± 9.24	29.5	< 0.001	55.66 ± 11	80.23 ± 6.75	10.3	< 0.001

Paired t test

Abbreviations: SF-36 36-Item Short-Form Health Survey, DAS28 Disease activity score, RA Rheumatoid arthritis, SLEDAI Systemic Lupus Disease Activity Index, SLE Systemic lupus erythematosus, PCS Physical components summary of the SF-36, MCS Mental components summary of the SF-36

psychological beliefs [34]. In the present study, a significant correlation was found between disease activity on one side, and physical and mental health scores on the other side, in both RA and SLE cohorts. This correlation was negative and strong with both the PCS and MCS components of HRQOL. This finding is consistent with those reported in other studies proving an effect of disease activity in RA and SLE patients on the HRQOL [4, 5, 12, 16, 34, 35]. These studies concluded the negative impact of both diseases on the patients' physical, emotional, and social functioning, and higher HRQOL and functional capacity at lower disease activity levels.

In the present study, at baseline, the SLE cohort had significantly better SF-36 subscale scores compared to the RA cohort during active disease. The same observation of this baseline difference was present in only one prospective study in a Mexican population [18]. The worse SF-36 scores among RA patients at baseline could be ascribed to high disease activity and the higher pain experience [36]. When in remission, the SF-36 scores were strongly improved in both cohorts. RA patients in sustained remission have been found to have better HRQOL and function, and lower rates of radiological damage compared with patients with higher disease activity states. This is the basis of the "treat to target" (T2T) strategy [37, 38]. Recently, a T2T approach for SLE was also established using remission criteria in SLE (DORIS) [24].

In the present study, a highly significant improvement was found in both the mean values of PCS and MSC scores for RA and SLE cohorts after remission. Studies done in RA patients showed that the PCS scores of the SF-36 questionnaire among patients with low disease activity were significantly higher when compared to those with moderate and high disease activity scores. This finding is in accordance with a study in Egypt, where a close relationship was found between the disease activity score and the magnitude of joint inflammation and destruction in RA patients with the scores of the physical domains of HRQOL [5]. The improvement of the MCS scores among RA patients after remission was also observed by Pascual-Ramos et al. who found a significant improvements in the VT and SF domains of the MCS among RA patients after remission [18]. The same was reported by Dalves et al. who found a significant improvement of both ER and MH domains of the MCS after remission [13]. The improvements in the current study were very large in the RA sample, which may be explained by the fact that we only included RA patients with sustained remission and not those with low disease activity.

In previous SLE studies, the PCS component of the SF-36 was found to be strongly related with SLE disease activity and organ damage [17, 33]. In the current study,

there was also a significant improvement in the MCS domain in SLE patients with sustained remission in comparison to those with active disease. In contrast to this result, in a prospective study done by Tsang-A-Sjoe et al. in SLE patients, the MCS scores at baseline and at last visit did not differ in patients with active disease and those in remission during the 2 years of the study [16]. The difference with our study may be explained by the strict inclusion criteria applied in our study, excluding SLE patients with current active neuropsychiatric lupus. Furthermore, our cohort is considering a different ethnic group. A difference between ethnic groups was also observed by Tsang A Shoe et al. who found that the MCS domain was positively associated with Caucasian ethnicity and that disease activity could differ between different ethnic groups [16].

The present study showed that a significant improvement in the SF-36 scores was observed in RA patients compared to SLE patients after remission in four subscales: general health, bodily pain, and physical functioning, while the opposite was true for the role participation with emotional health problems. The PCS component of the SF-36 scale aggregates the PF, RP, BP, and GH domains, which means that most of the PCS domains of RA patients were improved with remission. In the same time, a non-significant difference was found between the patients in remission from the two cohorts regarding all the MCS components scores. These observed findings related to SF-36 MSC and PSC component scores between the RA and SLE cohorts were also observed in a study by Pascual-Ramos et al. [18] where no significant changes were reported for the MCS component between the two studied cohorts. At the same time, RA patients in that study also scored better than SLE patients on the physical health component summary.

The smaller improvement of SF-36 scores among the SLE cohort compared to the RA cohort in the present study could be explained by the extensive physical, psychological, and social challenges faced by SLE patients. In addition, in other studies, the musculoskeletal manifestation of SLE was found to worsen the eight HRQOL domains especially, pain, fatigue, and burden to others [11, 39]. Another explanation could be the known musculoskeletal and mucocutaneous manifestations of SLE, besides the systemic inflammation affecting internal organs as the lungs, and heart, kidney, heart, and the GIT and sometimes causing neuropsychiatric symptoms [10, 11].

In a study done on 69 SLE patients in China, patients who remitted for 5 years or more were found to have a significant lower prevalence of renal involvement, leucopenia, or thrombocytopenia; moreover, it was associated with significantly better total health-related scores of the

Lupus Patient Reported Outcome [33]. An Italian study followed HRQOL in SLE patients who had been in remission. It was found that patients in prolonged remission for more than 5 years showed significantly better scores in the PF, RP, BP, GH, and SF components of the SF36 when compared with those in remission less than 5 years or unremitted [39].

The T2T strategy is a new treatment paradigm for RA and SLE patients that focuses on achieving remission or low disease activity score [40]. However, the effectiveness of the T2T approach in SLE patients has not yet been proven in a clinical trial, especially not for DORIS remission criteria [24]. Therefore, the study of patients in sustained remission (in accordance with valid T2T remission criteria) showing impact on outcomes as HRQOL, is essential to validate remission criteria.

A strength of our study is that we compared the correlation of disease activity with HRQOL in both RA and in SLE patients, which has hardly been done before in Saudi. A further strength of the current work is the assessment of impact not only of disease activity but also of the sustained remission criteria according to T2T approach in SLE and RA patients' mental and functional status. It is also a strength that it is the first or one of the first studies in a Saudi population.

A limitation of the present study could be the rather small sample size especially for the analyses of patients in remission. Not compared to control group. Also, the fact that only female patients were studied means that the results cannot be generalized to the total RA and SLE population; however, most of patients affected in both diseases are females. In addition, the study was conducted in only one center and in patients with Arab ethnicity and the study results may not be generalizable to different ethnicities.

Conclusions

Both SLE and RA patients in sustained remission strongly improved HRQOL domains. When in remission, RA patients had comparable or better HRQOL than SLE patients. Thus, it may be expected that early disease control and remission will be associated with better HRQOL outcome. Future prospective studies with a longer follow-up period are needed.

Abbreviations

SF-36: 36-Item Short-Form Health Survey; RA: Rheumatoid Arthritis, SLE Systemic Lupus Erythematosus; PF: Physical functioning; RP: Role physical; BP: Bodily pain; GH: General health; PCS: Physical component summary; RE: Role emotional; VT: Vitality; SF: Social functioning; MH: Mental health; MCS: Mental component summary; HRQOL: Health-related quality of life; ACR: American College of Rheumatology; SLEDAI: Systemic Lupus Disease Activity Index scores; ESR: Erythrocyte sedimentation rate; CBC: Complete blood count; Anti-CCP Abs: Anti-cyclic citrullinated peptide antibodies; RF: Rheumatoid factor; CMIA: Chemiluminescence microparticle immunoassay; ANA: Anti-nuclear antibodies; T2T: Treat to target

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Authors' contributions

BE collected the clinical data and contributed in writing the manuscript. AT analyzed and interpreted the patient data. DD gave the main idea, contributed in writing the manuscript, and interpreted the patient data. SA collected the data. ER collected and interpreted the clinical data. AA collected the data. MA contributed to the reference collection. PT contributed to collecting references and contributed in writing the manuscript. JR supervised and gave final approval. All authors read and approved the final manuscript.

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Availability of data and materials

The data is available upon request.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethical research committee at Al Hada Armed Forces Hospital, KSA (Registration number H-02-T-078), and performed according to the 1964 Helsinki Declaration. All patients had provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors have no financial or personal relationships or interests regarding this study.

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