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REVIEW

A review of health related quality of life in systemic lupus erythematosus

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Health-related quality of life (HRQoL) is an important outcome measure in patients with systemic lupus erythematosus (SLE). A review was undertaken of the literature relating to HRQoL in SLE. MEDLINE, EMBASE, CINAHL, Allied and Complimentary Medicine were searched to locate full papers in the English language reporting on HRQoL in adult SLE patients published between 1990 and 2005. In total 53 papers were included and the review was subdivided into: 1) description of HRQoL in SLE patients; 2) HRQoL and disease activity and/or damage; 3) the impact of other variables on HRQoL; and 4) HRQoL measures used in clinical trials in SLE patients. The findings were as follows: HRQoL is reduced in SLE patients; HRQoL is not correlated to disease activity or damage; age appears to have a negative impact on HRQoL especially physical health but the effect of disease duration is unclear; other potentially modifiable variables such as fatigue and psychosocial factors impact on HRQoL in a complex manner; and HRQoL measures which are sensitive to change should be an essential outcome measure in all clinical trials on SLE patients. *Lupus* (2006) **15**, 633–643.

Key words: health related quality of life (HRQoL); systemic lupus erythematosus (SLE)

Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune condition with an equally complex clinical presentation and course.[1–4] It can affect almost any organ system and is frequently an evolving disease with some manifestations developing over a period of months or even years. SLE can be challenging to diagnose as many of the non-specific features (fatigue, weight loss, low grade fever) can mimic other diseases and contribute to a diagnostic delay and distress experienced by the patient. The course of the disease is also variable and unpredictable.[1]

The survival of patients with SLE has significantly improved[5] but like many chronic diseases, there is currently no cure. Outcome measures in SLE therefore cannot just be confined to mortality data. In the evaluation of patients with SLE it is important to measure not only disease activity (which is potentially reversible with treatment) and damage (which is permanent and can be due to the disease or treatment) but also the patients' perspective[6] because the disease is likely to have a significant impact on many physical, social and psychological aspects of patient health and Quality of Life (QoL).[7] The term health related quality of life (HRQoL) refers to those aspects of life which are affected by health eg, functional status, and excludes other determinants of QoL eg, income, job security or living conditions.

Treatment of the more severe cases of SLE involves a balance between suppressing the signs and symptoms of the disease and minimizing the toxicities of the drugs used. With treatment, disease activity indices might improve but the patient might feel potentially worse due to the side effects of the medication. Measuring HRQoL provides patients with an opportunity to participate more fully in their treatment and ultimately facilitate better communication with the multi-disciplinary team of health professionals involved in their care.

Table 1 describes some of the more commonly used 'functional' and 'quality of life' measures.

There has been one previous review article on HRQoL in SLE. Gordon and Clarke[8] described the different tools available for measuring QoL, evaluating loss of productivity, use of health resources and also summarized the results of existing studies. A recent

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Table 1 Adult measures of functional status and quality of life

Measure/scale	*Content*	*No of items/scoring*	*Properties*
Modified Health Assessment Questionnaire (MHAQ)	Degree of difficulty, satisfaction with function over past six months and need for help in activities of daily living	Eight items (activities) within each subscale, Items are a subset of HAQ items *Separate scores for difficulty, satisfaction, change in difficulty, need for help* *Apart from satisfaction, higher scores = greater functional disability*	Function specific, translated into many languages, self- or interview administered, <10 minutes to complete
Quality of Life Scale (QOL-S)	Material goods, health, interpersonal relationships, self, recreational activities and independence	16 items *Higher score = better QoL*	Adapted for use in patients with chronic disease, translated into Swedish, measures quality of life rather than health-related quality of life, generic, self-administered, two to three minutes to complete
Arthritis Impact Measurement Scale-2 (AIMS-2)	Mobility, physical activity, dexterity, household activity, social activities, activities of daily living, pain, depression and anxiety, arm function, social support, work	101 items *Higher scores = poorer health*	Generic, translated into many languages, arthritis-specific, developed in patients with RA/OA, self-administered, 20–30 minutes to complete
Medical Outcomes Survey – Short Form 20 (SF-20)	Physical functioning, role functioning, social functioning, mental health, health perception, pain [SF-20+ has a question on fatigue]	20 items *Higher scores = better health except for pain and fatigue*	Generic, translated into many languages, self- or interview administered, five minutes to complete, evaluated in SLE patients, fatigue missing except for SF-20+ version
Medical Outcomes Survey – Short Form 36 (SF-36)	Physical functioning, role limitations due to physical problems, bodily pain, general health, social functioning, mental health, role limitations due to emotional problems, vitality	36 items (eight domains) *Higher score = better health*	Generic, translated into many languages, self- or interview administered, <10 minutes to complete, evaluated in SLE patients
Sickness Impact Profile (SIP)	Sleep and rest; eating; work; home management; recreation and pastimes; ambulation; mobility; body care and movement; social interaction; alertness behaviour; emotional behaviour; communication	136 series of statements describing different levels of health within each dimension *Higher scores = poorer health*	Generic, translated into many languages, self- or interview administered, 20–30 minutes to complete, not evaluated in SLE patients
WHOQoL-Bref	Physical, psychological, social and environmental	25 standardized questions *Higher scores = better QoL*	Generic, translated into many languages, self completion, 10 minutes to complete

review article by Seawell and Danoff-Burg[9] has elegantly summarised the literature on the psychosocial factors affecting SLE and behavioural interventions for these factors.

Review of the literature on health related quality of life (HRQoL) in SLE

The aim of this paper is to review the literature on the health related quality of life (HRQoL) in SLE patients. This has been subdivided into four major aspects:

1) Description of HRQoL in SLE patients.
2) HRQoL and disease activity and/or damage.
3) Impact of other variables including psychosocial factors on HRQoL in SLE.
4) HRQoL measures used in clinical trials in SLE patients.

A search of the literature using the following key word combinations was performed: 'SLE/lupus' with 'Quality of life', 'outcome measures', 'SF 36', 'well-being' and 'health status'. The following databases were searched: MEDLINE, EMBASE, CINAHL, Allied and Complementary Medicine on www.aditus.nhs.uk and also Medline on www.medscape.com. Limitations were imposed to publications relating to adults, in the English language and published since 1990 until 2005. 1990 was chosen as the start year as there are few publications on HRQoL in SLE patients prior to that. Publications relating solely to the development and/or validation of questionnaires will not be discussed. Neither will studies that have used unidimensional measures that concentrated mainly or solely on the physical[10] or emotional aspects of the disease[11–13] as we feel that these measures do not adequately assess HRQoL.

Description of HRQoL in SLE patients

Several authors have attempted to describe HRQoL in SLE. Two studies used multiple questionnaires to define HRQoL[14,15] but most studies used a single multidimensional questionnaire.[16–45] Five of these studies were longitudinal[41–45] and the rest cross-sectional. Many of these authors also correlated HRQoL with disease activity and damage.

HRQoL was found to be poorer in SLE patients in all the studies reviewed irrespective of the instrument used: the SF-20,[16,17] the SF-20+,[18,19] the SF-36,[20–27,42] the Sickness Impact Profile/Arthritis Impact Measurement Scale (SIP/AIMS)[28] and the Quality of Life Scale (QOLS).[29,30] Three of these studies[22–24] compared patients to normal control groups but the rest compared SLE patients to population norms.

Most studies used the SF-20 or SF-36 but the domains most negatively affected varied between the studies. In both studies by Sutcliffe *et al.*,[18,24] using the SF-20+ and SF-36 respectively, HRQoL was poorer in SLE patients in all the domains of both measures which was similar to the findings reported by Vu *et al.*[25] and Alarcon *et al.*,[42] both using the SF-36. In other studies, specific domains were more negatively affected than others such as role functioning (SF-20),[15] health perception, pain and role functioning,[18] all domains of the SF-20+ except social functioning[19] and all domains of SF-36 except emotional role limitation.[20,22] Using the SF-36, role physical, general health, vitality and role emotional were mainly negatively affected in one study[26] and physical functioning, role physical, bodily pain and general health in another.[21] When the composite score of the SF-36 was calculated, SLE patients had lower physical and mental scores[23,26,31] and were ranked in the 10th percentile for the physical component score (PCS) and in the 25th percentile for mental component score (MCS) when compared to a normative US population.[27]

Although the studies described above varied in the measures used, the ethnicity of patients studied and the numbers of patients recruited, HRQoL is undoubtedly impaired in SLE patients compared to population norms or controls. Most of the studies were conducted in outpatients who tend to have less severe disease and in spite of this, HRQoL was reduced. The SF-36 was the main tool used to measure HRQoL in SLE patients and this also allowed for the comparison of HRQoL between different rheumatological diseases. In the study by Thumboo *et al.*,[21] physical domains of the SF-36 were more negatively affected in SLE patients probably because inpatients were also recruited.

The poorer HRQoL in SLE patients is comparable to that found in severe medical illness,[46] Acquired Immunodeficiency Syndrome (AIDS),[47] Sjogren's syndrome (SS)[18] and rheumatoid arthritis (RA).[22,29] However, HRQoL was more affected in SLE patients compared to those with Wegener's granulomatosis (WG)[32] but less impaired when compared to those with fibromyalgia (FM).[30,33,34] SS, RA and WG are chronic autoimmune multisystem diseases and it is not surprising that SLE patients have similarly impaired HRQoL to these conditions. However, there were important differences between SLE and RA patients. The physical function and pain domains of the SF-36 were more affected in RA patients than SLE patients, perhaps not surprisingly because RA is a disease that primarily affects the joints.[22] In the study by Burckhardt *et al.*[29] using the QOLS-S and AIMS, SLE patients expressed more concerns about their disease compared to RA patients. Although on the whole both groups of patients

were satisfied with their quality of life there were some areas of dissatisfaction with their health that differed between the two groups. SLE patients focused on their symptoms of fatigue, their inability to plan ahead due to unpredictability of the disease, and the lack of understanding of the disease by their work mates and supervisors. Similar to the study by Gilboe *et al.*[22] RA patients focussed on their difficulty with mobility.[29] Using the Hoffman's Questionnaire for WG, Boomsma *et al.*[32] compared patients with SLE and WG. Even though WG can be a severe multisystem vasculitic disease, patients with SLE felt the disease had affected their daily living activities more severely than WG patients and were also more likely to resign from work than WG patients. On a positive note, SLE patients more often thought that their illness improved their relationship with friends compared to WG patients and brought their family closer together. Fibromyalgia, in which pain and fatigue are significant symptoms, has an important negative impact on quality of life. Patients with FM, whether primary[33] or secondary[30,34] had lower HRQoL compared to SLE patients without FM.

Irrespective of ethnicity, HRQoL in SLE patients was impaired but there were some important differences between the groups. Although many of the above studies had a multi-ethnic mix of patients, *comparison* between the ethnic groups was only described in three studies.[15,27,41] Devins *et al.*[15] investigated HRQoL in three ethnic groups (Whites, Blacks, Asian) using the Health Assessment Questionnaire (HAQ), Illness Intrusiveness Ratings Scale (IIRS), Affect Balance Scale (ABS), Center for Epidemiologic Studies Depression (CES-D) Scale and the Rheumatology Attitudes Index (RAI). Psychosocial well-being differed significantly across the three groups with whites reporting the highest and blacks the lowest levels. Illness intrusiveness (the extent to Which the illness and/or its treatment interfere with life domains) and educational attainment emerged as independent mediators for the race-related difference in the study[15] but the numbers of non-whites (17.3%) were small. Using the SF-36 in the Lupus in Minority Populations, Nature versus Nurture (LUMINA) study,[27] three ethnic groups (Hispanic, African American, and Whites) of fairly equal numbers were studied and baseline mental health was better in Whites than non-Whites although physical health was similarly impaired in all three groups. Thumboo *et al.*[41] studied three groups of patients, Chinese (85.6%), Malays and Indians also using the SF-36 and reported that ethnicity did not influence the HRQoL of this cohort of patients. The authors suggest that this lack of difference may be due to the fact that HRQoL is likely to be mediated by socio-economic factors and the study participants had a similar socio-economic status, thus having equal access to health care. Thus poor HRQoL in some ethnic groups may be a reflection of socio-economic influences. However, this relationship between ethnicity and socio-economic status is likely to be complex as suggested by the longitudinal study by Alarcon *et al.*[42] In this study,[42] African-American ethnicity was related to poorer HRQoL in only some subscales of the SF-36 but poverty and poor social support irrespective of ethnicity strongly predicted poorer HRQoL in all domains.

HRQoL and disease activity and/or damage

There are various standardized measures for SLE disease activity (Table 2). The most frequently used measures are the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),[48] variations of the Systemic Lupus Activity Measure (SLAM),[49] the British Isles Lupus Assessment Group (BILAG) index[50] and the European Consensus Lupus Activity Measure (ECLAM).[51] There is only one standardised index for damage, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI).[52] Cross-sectional studies are described in relation to the disease activity or damage measures employed followed by a description of longitudinal studies.

SLEDAI

Gladman *et al.*[14] reported no correlation between SLEDAI and the five instruments [SF-20, HAQ, Fatigue Severity Scale (FSS), Disability Days Measure (DDM), CES-D] employed. Two studies[16,17] reported no or weak correlation between SF-20 and SLEDAI. The SF-36 total score was also not correlated to SLEDAI.[34] Vu *et al.*[25] reported that higher disease activity on SLEDAI correlated to lower scores in two SF-36 domains, bodily pain and general health. Gilboe *et al.*[22] reported no correlation between the SF-36 and SLEDAI. A recent study[31] reported that SLEDAI weakly correlated to the physical component score of SF-36 but neither correlated to the mental component score of SF-36. Another recent study[35] employing the Mexican modified version of SLEDAI (Mex-SLEDAI) and World Health Organization Quality of Life-Abbreviated version (WHOQoL-Bref) as a measure of QoL, reported a negative correlation between higher disease activity and physical as well as psychological components of the QoL measure but not with the social or environmental components.

BILAG

The two studies by Stoll *et al.*,[19,20] reported weak correlations between the BILAG index components with

Table 2 Disease activity measures for systemic lupus erythematosus

Measure/scale	*Content*	*No of items*	*Scoring*
British Isles Lupus Assessment Group (BILAG)	Disease activity assessing eight organ systems over the last four weeks (subjective items including fatigue, arthralgia, myalgia)	86 items	Higher score greater disease activity
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)	Disease activity in the last 10 days assessing nine organ systems (no subjective items)	24 items	Higher score indicates more disease activity
Mex-SLEDAI	Modified version for use where estimation of dsDNA and C3 levels are not always available		
Systemic Lupus Activity Measure (SLAM)	Disease activity within the last four weeks assessing nine organ systems (subjective items include fatigue, myalgia, arthralgia) and seven laboratory items	32 items	Higher scores indicates more disease activity
SLAM-R/SLAM-2	SLAM-R/2 is revised SLAM with 31 items	31 items	
m-SLAM	m-SLAM is the SLAM without the laboratory components	24 items	
SLAM-F	Fatigue item removed	30 items	
SLAM-P	Patient version of SLAM	22 items	
European consensus lupus activity measurement (ECLAM)	Disease activity within the last four weeks assessing 10 organ systems (subjective items include arthralgia) and ESR and complement levels	33 items	Higher scores indicates more disease activity

some SF-20+ domains[19,20] and a slightly stronger but still weak correlation with the SF-36 domains.[20] In two of the studies by Thumboo *et al.*[36,37] SF-36 subscales also weakly correlated with BILAG scores.

SLAM and ECLAM

Sutcliffe,[24] reported that higher disease activity (SLAM-R) was negatively associated with all domains of SF-36 except role emotional and mental health. Dobkin *et al.*[38] subdivided SLE patients into two groups depending on disease activity (more active, SLAM-R ≥ 10 and less active, SLAM-R ≤ 10) and reported that patients with higher disease activity had a negative effect on all subscales of SF-36 except social function. Saba *et al.*[39] reported a significant negative correlation between SF-36 domains and the m-SLAM. Wang *et al.*[26] reported no correlation between SF-36 and SLEDAI but SLAM2 was associated with the general health subscale of the SF-36. In another study,[33] worse physical health (SF-36) was related to SLAM-R but there was no correlation between SF-36 and SLEDAI. Using the AIMS as a HRQoL measure, Burckhardt *et al.*[29] reported a strong correlation between SLAM-P and AIMS. In a recent study, Doria *et al.*[40] reported no correlation between SF-36 domains and ECLAM.

SLICC/ACR-DI

Fifteen cross-sectional studies examined the relationship between HRQoL and SLICC/ACR-DI. Only one[38] reported a *positive* correlation between damage and HRQoL and it was with the mental component summary (MCS) of the SF-36. The other studies reported no correlation or negative correlations: six studies reported no correlation between the SF-20[16,17] or the SF-36[33,34,36,40] and damage; one study reported a moderate negative correlation between damage and HRQoL (SF-36);[25] three studies, a weak correlation was reported between the SF-20+[20] or SF-36[20,22,37] and damage and the magnitude of the negative correlation between SF-36 and damage was not specified in four studies.[24,26,27,31] The domains of the SF-36 that were negatively associated with damage were predominantly the physical subscales.

Although the disease activity measures were different most studies reported that there were either no or weak correlations between disease activity or damage with HRQoL. There were minor differences depending on the disease activity measure used. The SLEDAI was the least likely to be correlated to HRQoL and this may be due to the fact that it has only objective items. The BILAG and the SLAM both measure some subjective items and thus the patients' views are inevitably taken into account. This is especially true for the modified SLAM, the m-SLAM from which objective laboratory results have been removed and SLAM-P which is a patient version of the SLAM. Another factor could be the time frame of the measures; the BILAG and SLAM relate to the same time frame as the SF-20 and SF-36, which is four weeks whilst the SLEDAI measures activity over the last 10 days. Even though there was only one measure for damage in SLE, there was

Table 3 Correlation coefficients between HRQoL and disease activity/damage in some of the studies

[Reference] Study population	*Measures*	*Comments*
[17] $n = 105$ (97 females) 76 Caucasians, 15 Blacks, 14 other races Cross-sectional, outpatients	SF-20 *SLEDAI* *SLICC/ACR-DI*	SLEDAI weakly correlated to SF-20 social functioning ($r = -0.34$) and health perception ($r = -0.3$), [$P = 0.004$ for both] No correlation between damage and any domains of SF 20 ($r = -0.27$ to -0.03)
[16] $n = 96$ (86 females) 87 Caucasians, 3 Asians, 2 blacks, 4 Native Americans Cross-sectional mostly outpatients (11 inpatients)	SF-20 *SLEDAI* *SLICC/ACR-DI*	No correlation between SF-20 and SLEDAI ($r = -0.18$ to -0.01) No correlation between SF-20 and damage ($r = -0.24$ to -0.05) except health perception ($r = -0.34$, $P = 0.02$)
[19] $n = 141$ (133 females) 97 Caucasians, 16 Afro-Caribbean, 22 Asians, 6 mixed Cross-sectional, outpatients	SF-20+ *BILAG*	BILAG musculoskeletal associated with physical functioning, pain and health perception ($r = -0.23$, -0.29 and -0.47 respectively, $P < 0.01$ for all three), BILAG neurological correlated with social functioning ($r = -0.27$, $P < 0.01$)
[20] $n = 150$ (143 females) 109 Caucasians, 17 Afro-Caribbean, 21 Asians, 3 mixed Cross-sectional, outpatients	SF-20+, SF-36 *BILAG* *SLICC/ACR-DI*	SF-20+ and SF-36 weakly correlated to BILAG ($r = -0.27$ to -0.37 and -0.27 to -0.40 respectively, $P < 0.01$ for all). A weak correlation was also found between the physical function subscale of both measures and damage ($r = -0.32$ and -0.30, $P < 0.0001$)
[36] $n = 118$ SLE (112 females) English-speaking, 100 Chinese, 14 Malays, 4 Indians Cross-sectional, inpatients and outpatients	SF-36 *BILAG* *SLICC/ACR-DI*	SF-36 subscale scores weakly correlated with BILAG scores ($r = -0.37$ to 0.15). Body pain, role physical and role emotional weakly correlated to BILAG Musculoskeletal ($r = -0.37$, -0.31 and -0.21, $P < 0.05$ for all three) and social functioning weakly correlated to BILAG Mucocutaneous ($r = -0.25$, $P < 0.01$) No correlation between SF-36 domains and damage
[34] $n = 119$ SLE (of whom 25 had FM) (109 females) 90 Caucasian, 11 Black, 18 others Cross-sectional, outpatients	SF-36 *SLEDAI* *SLICC/ACR-DI*	No correlations betweeen SLEDAI and SF-36 ($r = -0.27$ to 0.20) No correlation between damage and SF-36 ($r = -0.24$ to 0.09)
[43] $n = 96$ (86 females) 76 Caucasians, 20 unspecified Longitudinal (monthly for 4–6 months) Outpatients	SF-36, HAQ *SLAM-R, SLEDAI* *SLICC/ACR-DI*	SF 36 subscales except role emotional associated with SLAM–R ($r = -0.29$ to -0.41, $P < 0.05$). However, only SF-36 subscales vitality and social function associated with SLEDAI ($r = -0.26$, $P < 0.01$, other correlations ranged from $r = -0.03$ to -0.20)

no consistent association between HRQoL as measured by either SF-20 or SF-36 and the SLICC/ACR-DI. For both disease activity and damage, most authors tend to report significant correlations based on *P*-values rather than the strength of the correlation itself. This can be misleading as statistical significance is potentially determined by sample size. From the observed correlation coefficients it is evident that the relationship between disease activity/damage and HRQoL is at best weak. The results of seven studies have been tabulated[16,17,19,20,34,36,43] (Table 3) to illustrate the correlation coefficients and *P*-values, where appropriate, with the various disease activity measures used.

All the studies mentioned so far are cross-sectional and therefore can only suggest but cannot confirm or determine a causal relationship between disease activity or damage and QoL.[26] Longitudinal studies may be more helpful in this respect[41–45] and will be described below.

The study conducted by Fortin *et al.*[43] over four months examined correlations between SF-36 and disease activity (SLAM-R, SLEDAI) or damage at baseline and at monthly intervals. Similar to findings of cross-sectional studies, baseline SLEDAI showed no correlation to subscales of SF-36 whilst SLAM-R correlated with physical function, bodily pain, vitality and general health but not to social function or mental health subscales of the SF-36. Increase in disease activity over time led to worsening all domains of the SF-36 (except bodily pain when SLEDAI was used). Damage at baseline predicted only a poorer physical function with time but the other domains of SF-36 were unchanged. However, longer disease duration and higher education predicted better role emotional of the SF-36 suggesting that patients with time learn to cope with the disease.

Although the above study by Fortin *et al.*[43] suggested that disease activity but not damage predicted HRQoL, this was not confirmed by four other studies. Gilboe *et al.*,[44] reported that HRQoL and disease activity remained unchanged after two years despite progression of damage. In another study[45] spanning 15 months the patients significantly improved from baseline in terms of fatigue and the physical aspects of HRQoL (PCS of the SF-36) despite the fact that disease activity changed (worsened in 40.9%, improved in 50.5% and remained

the same in 8.8% of patients). In the study by Thumboo *et al.*,[41] the physical aspects of HRQoL were not predicted by disease activity or damage but mental health improvement was associated with less damage and in a complex manner to disease activity. Other variables such as learned helplessness and family support were also important.[41] Disease activity and damage had little influence on the subsequent HRQoL of the patients in the study by Alarcon *et al.*[42] Instead, poor self reported HRQoL was found to be consistently predicted by older age while other variables, fibromyalgia, helplessness, fatigue and abnormal illness behaviours, were also predictive but less consistently.[42]

The longitudinal studies do suggest that with time HRQoL especially psychological health in SLE patients improves. The improvement of HRQoL with time also suggests that some aspects of HRQoL may be amenable to intervention. Burckhardt *et al.*[29] found that the AIMS psychological variable strongly predicted the QoL and therefore it is important to identify and treat depression/anxiety to improve the QoL of the patient. The study by Saba *et al.*[39] noted that patients in remission scored higher in the emotional and mental health domains than normative mean values and suggested that this could be because these patients were reviewed regularly and thus depression and other aspects of mental health were likely to be identified and treated promptly. Thus clinicians should be resolute in their attempts to treat not only the physical aspects of the disease but also the psychological features.

From the various studies, cross-sectional and longitudinal, HRQoL is a different entity to that of disease activity and damage and thus all three aspects should be measured in a patient with systemic lupus erythematosus to obtain the complete clinical picture.

The impact of other variables on HRQoL

Various other factors may mediate levels of HRQoL. Although socioeconomic factors have been implicated this will not be included in this review paper due to the complexities related to different health care systems in the countries studied. The factors considered are fatigue, social support, role strain, coping, stress,illness intrusiveness, educational attainment, helplessness, age and disease duration (ethnicity has been discussed previously).

Fatigue

Fatigue is a very common symptom in SLE and its impact is worthy of assessment despite the fact that it is non-specific.[53–57] and in the studies many patients felt that it was their most debilitating symptom.[10,54,58,59] One of the major problems with the literature on fatigue in SLE is that different measurement tools are used in the various studies making it difficult to make comparisons and reach conclusions. Few HRQoL measures included fatigue as a domain. The SF-20 + is a modified measure which includes fatigue as an item[19] and it also appears as a subscale in the SF-36 as 'vitality'.

From the various studies using the Fatigue Severity Score (FSS)[53,54,56–58,63] the Chalder Fatigue Scale (CFS),[55] the Piper Fatigue Scale (PFS),[62] the Multidimensional Fatigue Inventory (MFI),[61] the Vanderbilt Fatigue Scale (VFS)[57] and other *ad hoc* measures,[59,60] fatigue is reported to be prevalent in SLE patients ranging from 50 to 85.7%.[53,56,58–60] When compared to controls, two studies have shown that SLE patients experience higher levels of fatigue.[61,62] whilst another[55] reported that fatigue levels were similar in SLE patients and healthy controls. In spite of the prevalence of fatigue in SLE patients only two studies examined the correlation between HRQoL and fatigue and authors from both studies reported a negative impact on all domains of the SF-20[54] and the SF-36.[53]

Social support

Sutcliffe *et al.*[24] reported that a higher level of social support was associated with better HRQoL (SF–36) except for the role physical domain. Higher patient satisfaction with health care was also associated with better general health of the SF-36.

Role strain, coping, stress, illness intrusiveness, educational attainment, helplessness

Karasz and Ouellette[64] reported that SLE negatively affected psychological well-being by causing depression and demoralization because there was impairment of role strain (when the impact of the disease on the patient's social role becomes too great or when the disease traps the patients in a social role they would rather not be in).

In the cross-sectional study by Dobkin *et al.*,[38] irrespective of disease activity, coping featured in the variables as a predictor of both the physical and mental aspects of the HRQoL (SF-36). In the less active state, predictors of better mental health were less stress, less emotion-oriented coping and more task-oriented coping whilst better physical health was predicted by less stress and younger age. In a more active disease state, better mental health was predicted by more education and less emotion-oriented coping whereas better physical health by more emotion-oriented coping. In a Dutch study of a small group of SLE and RA patients, Wekking *et al.*[65] examined prospectively

the relationship between stress and physical and psychological aspects of health using the Dutch versions of EPCL (Everyday Problem Checklist) and AIMS. The authors found that the number and intensity of daily stressors were negatively correlated to physical and psychosocial status in SLE but this was not so with RA patients.

Devins *et al.*[15] found illness intrusiveness and educational attainment were independent mediators of the race-related differences (blacks with worse health and whites the best) in psychosocial well-being as measured by the Affect Balance Scale. The authors surmised that the cultural differences such as symbolic significance of disease, stigma associated with disease, culturally based health beliefs between patients and health care providers could account for this difference between the races. Helplessness (which is a belief that nothing the person does or can do will change the course of the disease) was negatively associated with physical health of the SF-36[41] and helplessness, fibromyalgia, fatigue and abnormal illness behaviours predicted poor HRQoL in whites, Hispanics and African-Americans.[42] High stress, poor social support and psychological distress were associated with poor HRQoL in SLE patients in another study.[66]

In summary, the studies suggest that variables such as fatigue, social support, helplessness, coping style, illness related behaviours, role strain mediate the effect of the disease on HRQoL and support biopsychological intervention to improve HRQoL. In addition these variables could also be interlinked. It has been suggested that fatigue may be secondary to abnormal illness behaviours and helplessness[56,57] or sleep disorders (sleep disruptions and/or sleep anxiety).[62] Thus, in the management of SLE patients with fatigue, other aspects such as sleep problems and depression may need to be addressed and a study has shown that when depression and stress decreased, fatigue improved.[45] Sutcliffe *et al.*[24] reported that better health status could be further improved by providing better social support and satisfaction with health care. Thumboo *et al.*[41] also reported similar findings in that improved mental health of the SF-36 after six months was associated with better family support. Dobkin *et al.*[38] concluded that a multi-disciplinary approach which incorporates teaching different coping strategies to help patients adjust to the impact disease activity has on their mental and physical health may improve HRQoL in SLE patients. Studies of behavioural interventions have been summarised by Seawell and Danoff-Burg.[9]

Age and disease duration

Sixteen papers examined the impact of age on HRQoL, 13 of these papers employed the SF-36,[22–25,27,33,38,40–44,66] one each employed the S F-20,[20] AIMS[29] and SIP/AIMS.[28] Ten studies,[20,22,23,27,28,33,40,42–44] reported a negative correlation between age and physical health. One study[42] reported a negative correlation with mental health and one a positive correlation.[41] Four studies reported no correlation between age and HRQoL.[24,25,29,66]

The relationship between disease duration and HRQoL was examined in ten papers. Longer disease duration correlated to better physical health,[41] better mental health.[27,42] and better role emotional[43] in some studies. However, in another disease duration correlated to better HRQoL (SF-36) *except* for role emotional and mental health subscales[25] and one study reported worse physical health with longer disease duration.[20] Some investigators found no correlation between the two.[22,24,40,66]

Overall, age appears to have a negative effect on HRQoL especially physical health but the effect of disease duration is unclear.

HRQoL measures used in clinical trials in SLE patients

Various outcomes have been used in SLE clinical trials including a variety of clinical features (fatigue), laboratory indicators (dsDNA levels, complement levels), disease activity measures, damage scores, QoL measures, health care utilization and socio-economic factors.[67–69] It is important to employ HRQoL measures in clinical trials as they are just as relevant as but separate from disease activity and damage indices in informing choice of therapy, managing symptoms, formulating interventions and may facilitate justifying the considerable costs of new therapies. And indeed HRQoL measures have been recommended to be incorporated into the core data set for observational studies and clinical trials.[70]

From the literature there are only six clinical trials that reported the use of HRQoL (Table 4) and all six employed the SF-36.[71–76] In spite of the fact that the SF-36 is a generic measure it has been recommended as the HRQoL outcome measure for future clinical trials in SLE.[77] In addition, the HRQoL tool used should also be sensitive to change but from these six studies, it was unclear if the SF-36 displayed sensitivity to change and clearly further studies to examine that should be undertaken.

Summary

Most studies have employed generic questionnaires such as the SIP, SF-20 and the SF-36 to describe HRQoL in SLE. The SF-36 is the most frequently used

Table 4 HRQoL in clinical trials on SLE patients

[Reference] Study population	*Authors' conclusion with regards to HRQoL (all studies used SF-36)*
[71] Partially randomised placebo-controlled, double-blind, dose-ranging trial to evaluate optimum dose of LJP 394 58 patients (53 female) completed (49 LJP 394, nine placebo)	No SF-36 results presented or discussed
[72] Double-blind, placebo-controlled cross-over trial to determine if low dose UVA-1 cold light treatment is able to reduce disease activity in SLE 11 patients (one male) with mild to moderate SLE	Total SF-36 scores similar following treatment and placebo. Vitality domain improved after UVA-1 (−15.91 points from 33.64 to 49.55, 95% CI −29.58 to −2.24) when compared to placebo (2.27 points from 47.27 to 45.00, 95% CI −8.60 to 13.14) [$P = 0.03$]
[73] Randomized controlled trial to evaluate the effect of brief supportive expressive group psychotherapy as an adjunct to standard medical care 124 patients (all females) completed (58 treated, 66 controls)	Intervention did not influence the physical (−0.14, 95% CI −3.18 to 2.90) or mental components (−1.38, 95% CI −4.57 to 1.81) of the SF-36 at 12 months follow-up compared to control group Data does not support the use of this intervention
[74] Randomized control trial of LJP 394 or placebo in patients with renal disease 230 patients randomised (114 LJP 394, 116 placebo) 179 completed study (87 LJP 394, 92 placebo) [Gender breakdown not specified]	The intervention group at 16 weeks improved in role emotional (+7.3 versus −8.2, $P < 0.01$), social functioning (+4.3 versus +0.7) and role physical (+11.3 versus +6.0) domains of the SF-36 compared to the control group In 37 patients with data pre- and post-renal flares, prior to flares, those receiving LJP 394 reported stabilization or improvement in all domains except pain compared to deterioration of all domains with placebo. Following flares, changes in role emotional domain scores differed by 22.7 points between the two treatment groups favouring LJP 394 treatment
[75] Randomized control trial to evaluate a theory-based intervention to improve patient self-efficacy and partner support to manage SLE 122 patient (three males)/partner randomised (64 intervention, 58 control)	At 12 months the SF-36 global mental score was higher (69 versus 58, $P < 0.04$) for patients in the intervention group
[76] To evaluate the efficacy of low dose dehydroepiandrosterone (DHEA) on HRQoL in glucocorticoid treated female patients with SLE Randomised double-blind placebo-controlled study for six months followed by six months open DHEA treatment 37 females patients completed study (20 DHEA, 17 placebo)	Compared to baseline levels, at six months, DHEA group improved in role physical and role emotional domains ($P < 0.05$) which was not completely sustained at 12 months. The change in role emotional after the six months was significantly better in the DHEA group (+23.3 ± 37.6) compared to the placebo group (−14.6 ± 40.2, $P < 0.01$). Role physical improvement was not significantly better than for all patients placebo. MCS score improved significantly in the DHEA group between baseline and six months (53.9 ± 24.4 to 62.4 ± 17.9, $P < 0.05$) with a decrease at 12 months which was not significant. In the open study, the placebo group (given DHEA) improved in mental health ($P < 0.05$)

in SLE populations and has the advantage of being useful for comparing the HRQoL in SLE to that of other disease populations and normal controls. As with other generic questionnaires some important domains for SLE patients are notably absent eg, sleep and sexual functioning and this may make it less sensitive.[26] Sleep disturbances are frequent in SLE patients and may impact on fatigue[78,79] which in turn can affect HRQoL. SLE patients also have a higher rate of sexual dysfunction compared to controls.[80] Therefore attention has recently turned towards developing a disease specific questionnaire for patients with SLE with a view to including domains not previously addressed in generic measures. Patients should also be the source of items for any HRQoL instrument and this approach has the benefit of assuring the instrument's acceptability and relevance to SLE patients.[81] Although a group from Singapore has recently published on the development and validation of a SLE disease-specific HRQoL measure, the SLEQOL, patients, however, were *not* the source of item generation.[82] On the other hand, we have developed and validated a *patient-derived* SLE specific HRQoL measure, the LupusQoL, for use in adults with SLE.[83] The comparison between the two measures is beyond the scope of this review paper. However, as SLE patients were the source of the items for the LupusQoL,[83] this will ensure that all the areas that these patients consider to be important are included and provide a more meaningful assessment of HRQoL in these patients than is currently available.

In conclusion:

1) HRQoL is reduced in SLE patients and is comparable to severe medical illnesses (AIDS, SS, RA, WG). Fibromyalgia patients have poorer HRQoL than SLE patients.
2) HRQoL is not well correlated to disease activity or damage. Thus, the three outcome measures (disease activity, damage and quality of life) are mainly independent of one another and all three should be

assessed in a patient with SLE to capture the complete clinical picture.

3) Other factors such as age, disease duration, fatigue and psychosocial factors impact on HRQoL in a complex manner. In particular, fatigue is a potentially modifiable variable which can have an important negative impact on HRQoL in SLE. However, it is not always included in HRQoL measures and in SLE this is a major omission due to its high prevalence.
4) HRQoL measures which are sensitive to change should be an essential outcome measure in clinical trials on SLE patients.

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