Quality Of Life and Fatigue in Patients with Systemic Lupus Erythematosus

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Abstract

Background: patients' quality of life and disease activity measurements in SLE are necessary for optimal patient care. They are central to clinical guidelines and treat-to-target approaches, which have been shown to improve outcomes in SLE, and rely on specifically defining and measuring low disease activity and remission. Disease exacerbations or flares in SLE span in range of severity from mild or moderate episodes that can be managed in the clinic to life threatening flares that require hospitalization. These flares place patients at risk for permanent organ damage, are associated with significant morbidity, and contribute to increased healthcare costs. Limiting the frequency and severity of flares has been an ongoing objective in SLE disease management, with extensive research focused on assessment of imminent flare risk and development of flare prediction biomarkers. SLE patients experience events related to disease activity, irreversible damage, and medications' side effects which may negatively impact their HRQoL and eventually may result in disability (25%-57%). Thus, their evaluation should include disease activity, severity and HRQoL. HRQoL in SLE is lower than in the general population and in patients with other common chronic diseases and comparable to that of other severe medical illnesses, such as the acquired immunodeficiency syndrome (AIDS), Sjögren´s syndrome and rheumatoid arthritis; however, it is less impaired than in fibromyalgia.

Keywords: Quality Of Life, Fatigue, Systemic Lupus Erythematosus

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Introduction

The World Health Organization (WHO) defines quality of life (QoL) as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". It is a broad concept affected by the individual's physical health, psychological state, personal beliefs, social relationships and their relationship with the environment. In clinical medicine, health-related quality of life (HRQoL) is used as a multidomain concept indicating the overall impact a disease and its treatment have on the individual´s ability to function and their perceived well-being in the physical, mental and social life domains **(1)**

The Need to Assess HRQoL in SLE

SLE patients experience events related to disease activity, irreversible damage, and medications' side effects which may negatively impact their HRQoL and eventually may result in disability (25%-57%). Thus, their evaluation should include disease activity, damage and HRQoL. HRQoL in SLE is lower than in the general population and in patients with other common chronic diseases and comparable to that of other severe medical illnesses, such as the acquired

immunodeficiency syndrome (AIDS), Sjögren´s syndrome and rheumatoid arthritis; however, it is less impaired than in fibromyalgia **(2).**

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommended five core domains to be evaluated in SLE clinical studies, namely disease activity, damage, HRQoL, adverse events and economic impact. Similarly, EULAR recommends assessing HRQoL at each clinic visit to determine the burden SLE exerts on patients. This recommendation reflects the fact that HRQoL correlates poorly with disease activity and damage accrual **(3).**

In fact, HRQoL, disease activity and damage reflect different domains impacted by lupus, and all should be assessed to obtain a complete assessment; this provides additional discriminatory power when assessing new therapies. These measures may be independent of each other. Furthermore, therapeutic interventions may improve disease activity but may have limited to no impact on the patient's HRQoL which tends to be stable over time. In contrast, disease activity may change rapidly, especially during flares or in patients with a relapsing-remitting pattern while organ damage gradually accumulates over time (**4).**

Elements of HRQoL

The effect of a disease on the patients' perception of their physical, psychological, and social functioning constitutes HRQoL. Additionally, HRQoL reflects the extent to which hopes and expectations are matched by experience, the patients' perceptions of their position in life considering the context of the culture and value systems where they live, the appraisal of one's current state against some ideas and things that individuals regard as important (**5).**

WHO has proposed a tool to measure all six HRQoL domains which in turn have specific elements: physical (pain, discomfort, energy and fatigue, sleep and rest); psychological (positive feelings, thinking, learning, memory, concentration, self-esteem, body image and appearance, and negative feelings); level of independence (mobility, daily activities, dependence on accompaniment or treatment and work capacity); social (personal relationships, social support, and sexual activity); environmental (physical safety and security: the home environment, financial, health care, social care, recreation/rest, physical environment, and transport); and spirituality (spirituality, religion, personal beliefs) (**6).**

How to measure HRQoL in SLE

HRQoL can be assessed with generic and disease-specific questionnaires. Generic QoL questionnaires are used in the general population's healthy and diseased individuals. Their advantage is that the scores obtained in different populations and conditions can be compared allowing the measurement of disease burden and health resources allocation. In addition, many generic questionnaires have undergone extensive validation and have been adapted to multiple languages and cultures. However, a disadvantage to use them alone is that they may inadequately ascertain QoL dimensions specific to lupus patients, such as physical appearance and fertility. Furthermore, generic instruments may not be sensitive enough to capture the fluctuations in health status observed in SLE patients. In contrast, disease-specific questionnaires tend to be more sensitive to change and are more appropriate to evaluate specific therapeutic interventions in clinical trials. Both types have been used in patients with lupus (**6).**

LupusQoL

This is the most widely studied SLE-specific HRQoL measure, developed and validated in SLE adults from the United Kingdom (UK). Since then, it has been validated in a sample of united states (US) patients. Likewise, a Spanish version has been adapted and validated. The LupusQoL has also been translated into 77 languages for use in 51 countries; it consists of 34 items derived from SLE patients and grouped into eight domains: physical health, emotional health, body image, pain, planning, fatigue, intimate relationships and burden to others. The questions refer to the patient's experience over the preceding four weeks; responses are given on a 5-point Likert scale (0-4, where 0 means all the time and 4 never). A summary LupusQoL score is reported on a scale of 0 to 100, with higher values indicating a better HRQoL, 0 representing the worst HRQoL and 100 the best HRQoL. As for the respondent burden, the time to complete is less than 10 minutes (**7).**

SLEQOL

The SLEQOL was originally developed and validated in English-speaking Singapore SLE patients to assess their HRQoL. It includes 40 items grouped into six domains: physical functioning, activities, symptoms, treatment, mood, and self-image. These items were generated by rheumatologists and nurse practitioners, not by patients. The questions

pertain to the patient's experience over the previous week and are answered with a 7-point Likert scale. The total score is the sum of all responses across all domains, ranging from 40 to 280, with higher values corresponding to worse QoL. As for the respondent burden, the time to complete this questionnaire is less than five minutes (**3).**

L-QoL

The L-QoL is a SLE-specific HRQoL measure developed using a needs-based QoL model, which postulates that life gains in terms of its quality result from the ability and capacity of individuals to satisfy their needs. Its validation has been assessed in a UK SLE sample and, recently, in a Turkish population. L-QoL comprises 25 items that assess the overall effects of SLE and its treatment on QoL. This tool was derived from qualitative interviews with SLE patients exploring the impact of their disease. Each question is answered as true/non-true; the scores range from 0–25, with higher scores indicating worse QoL. The questionnaire is easy to complete taking less than five minutes (**8).**

Predictors of HRQoL

SLE-related manifestations

A low baseline QoL is an important predictor of a poor subsequent QoL. In terms of the relationship between disease activity and QoL, there are variable results, as already noted. Some possible explanations for this could be the use of nonspecific scales to assess HRQoL and of different tools to ascertain disease activity, the heterogeneity of lupus, and the role of socio-demographic (age, educational level) and behavioral (coping with illness) factors that modulate disease activity **(9).**

On the other hand, the use of the LupusQoL has shown a more consistent inverse correlation between disease activity and QoL. A lupus low disease activity state (LDAS) as recently defined has been associated with a better HRQoL in a multinational Asian study of 1422 patients. Moreover, in a study from Perú, the use of immunosuppressants, as a probable surrogate of higher disease activity, associated with worse scores in some of the LupusQoL domains such as physical health, pain, planning, burden to others, emotional health and body image; this could also be due to the impact of medications' adverse events on HRQoL **(10).**

Comorbidities

Fibromyalgia, occurring in 9.5% to 35.7% of lupus patients, is an independent and important HRQoL predictor. Likewise, SLE patients with anxiety and depression present a low HRQoL; that is particular the case with depression. Both are relatively frequent in SLE patients with prevalence rates of 24% and 37%, respectively. Interestingly, depression has been related to disease activity levels as assessed by the Systemic Lupus Activity Questionnaire (SLAQ) or by the Patient's Global Assessment (PGA); that has not been the case with the SLEDAI. Also, patients with depression and SLE experience greater work disability. Finally, patients with the metabolic syndrome (MetS) have been found to have lower levels of functioning than those without it in a cross-sectional study encompassing 100 Italian SLE patients **(11).**

Impact of HRQoL: HRQoL affects several aspects of the patients' lives including how to deal with stress, their intimal relationships, their work- and home-related activities and their adherence to treatment. They, oftentimes, experience variable degrees of physical and mental limitations; they can face these limitations by intentionally minimizing their impact (coping) or maximizing it (catastrophizing). A poor mental component of HRQoL is associated with a higher catastrophizing score, which may turn to be a two-way interaction: poorer HRQoL increases catastrophizing, which worsens pain and depression reducing further the patient's HRQoL. As to intimal relationships, women with SLE present a lower sexual function than healthy controls whereas a better HRQoL is associated with a better sexual function (**12).**

Poorer HRQoL, particularly its physical component, is associated with work disability; the relationship between HRQoL and work disability is bidirectional, better HRQoL allows the patient to work; in turn, work makes the patients feel better. Poor HRQoL is also associated with work productivity impairment, activity impairment and activity of daily living (ADL's) difficulties; oftentimes, patients may need help from family and/or friends.

Fatigue in SLE patients

Fatigue can be defined either as a progressive impairment of the force generating capacity of muscle (peripheral or muscle fatigue) or as a lessened capacity for work and reduced efficiency, usually accompanied by feelings of weariness, sleepiness, and irritability **(13).**

Fatigue is a subjective symptom which is difficult to assess and manage during the disease course of SLE patients. Clinical assessments by physicians generally include objective disease activity and damage scales but patient perceptions of disease burden also include coexisting factors, such as fatigue, fibromyalgia, anxiety and depression. Fatigue is reported to be the most disabling factor by patients, therefore examining the factors of fatigue is important in clinical practice. In a study by Sterling et al., (14) patients with SLE described fatigue as having an impact on multiple aspects of their life, such as social and family activities, emotions, cognition, work and activities of daily living.

Overman et al. (15) studied severe fatigue in a broad range of rheumatic diseases and reported severe fatigue present in 41–57 % of patients with a single inflammatory rheumatic disease. Fatigue was least prevalent in patients with osteoarthritis and most prevalent in patients with fibromyalgia.

The effect of MSK flares and depression on physical health impairment is largely mediated by fatigue. Thus, the patient's perception of disease activity as measured by physical health is largely influenced by fatigue. In addition, fatigue has a significant negative impact on QoL of SLE patients with depression. (**16)**

Relationship between fatigue and disease activity

In the study by Pettersson and his colleagues, although the median SLEDAI score of their SLE group was 0, patients with SLE were more exhausted than healthy controls. Mean multidimensional assessment of fatigue (MAF) scores of patients were lower than some previous studies **(17).** Low disease activity could be responsible for lower MAF scores of their patients.

Pettersson et al. (17) showed higher levels of fatigue in patients with higher disease activity assessed by systemic lupus erythematosus activity measure (SLAM) and reported that incongruent associations between disease activity and fatigue in different studies may depend on which measures of disease activity are used. Fatigue is one of the subjective items included in SLAM and this is reported as a possible reason of positive association between fatigue and disease activity in this study. In another study, measuring disease activity with both SLEDAI and SLAM in SLE patients, the authors reported an association of fatigue with disease activity as measured by the SLAM but not with the SLEDAI score (**18).**

In comparison with other scales utilized to measure disease activity, SLEDAI also has a shorter timeframe with 10 days, and this could be a disadvantage in capturing the relationship between fatigue and disease activity. On the other hand, disease activity scores including subjective parameters could lead to overestimation of the relationship between disease activity and fatigue (**18).**

Factors affecting fatigue.

The MAF scores may be affected by smoking. In a study from Sweden, patients with SLE that experienced lower levels of fatigue had fewer smokers than higher and intermediate groups **(17).**

Yilmaz-Oner et al. (19) has pointed out that the severity of fatigue is correlated with physiological distress and Health-related quality of life (HRQOL) of patients. Higher levels of depression and anxiety were observed in the SLE group and Hospital Anxiety and Depression Scale A (HADS-A) and Hospital Anxiety and Depression Scale D (HADS-D) scores significantly correlated with the General fatigue index (GFI).

A study by **Storm Van's Gravesande et al., (20**) showed that unexplained fatigue and depression might act as independent risk factors for each other in general health care.

It was reported that fatigue was more strongly associated with neuropsychiatric symptoms in comparison to clinical signs and symptoms of the diseases. Psychosocial distress also predicts QoL in SLE; therefore, anxiety and depression may contribute to the degree of fatigue with an alternative way via worsening the QoL of patients. The nature of the disease with unpredictable flares and the probability of involving multiple organ systems might be the causes of the increased prevalence of anxiety and depression in SLE patients. The other factors causing anxiety and depression may be the lack of knowledge about the disease, treatment and expected outcomes of SLE**.** The effect of educational level on fatigue may be variable. Some studies revealed no effect (**19**).and others stated that higher fatigue scores in patients with lower education and concluded that lower education may affect a patient’s ability to understand the course of the disease and treatment **(21).**

Anxiety and depression are included among the neuropsychiatric lupus syndromes by ACR and Yilmaz-Oner et al,(**19**) suggest that psychiatric assessment of patients with severe fatigue would be useful to reveal possible confounding mood disorders and/or neuropsychiatric lupus. There is a relationship between reduced QoL and the degree of fatigue in SLE, as indicated by **Olesińska and Saletra (22).** The decreased HRQoL may be an outcome or predictor of fatigue in SLE patients. It is also possible that other causes, such as psychosocial factors, fibromyalgia, sleep disorders, helplessness, and abnormal-illness behavior may be associated with poor QoL in SLE patients.

Assessment of fatigue in SLE patients

Since fatigue may be influenced by a variety of factors and because of the diverse profiles of fatigue in SLE, the management of fatigue should rely upon an individualized person-centered approach. Women with SLE have reported the need for fatigue acknowledgement by clinicians, as well as conversations about fatigue, with information about coping strategies **(23).**

Assessment of fatigue in SLE patients

Fatigue management in SLE would start with an assessment of the intensity and the characteristics of fatigue using validated scales, enabling an individual follow-up of fatigue over time. In recent years, there has been an increasing interest in using Patient Reported Outcomes (PROs), because they place the patients at the center of their health management and help to establish a trusting physician-patient relationship. The most commonly PROs used to evaluate fatigue in SLE are the Fatigue Severity Scale (FSS), the Functional Assessment of Chronic Illness Therapy (FACIT-fatigue score), which we use in clinical practice, the Fatigue- visual analogue scale (VAS), which are unidimensional scales measuring fatigue intensity, and the Multi-dimensional Fatigue Inventory (MFI), which analyze general fatigue, physical and mental components of fatigue as well as the reduction in activities and motivation (**24).**

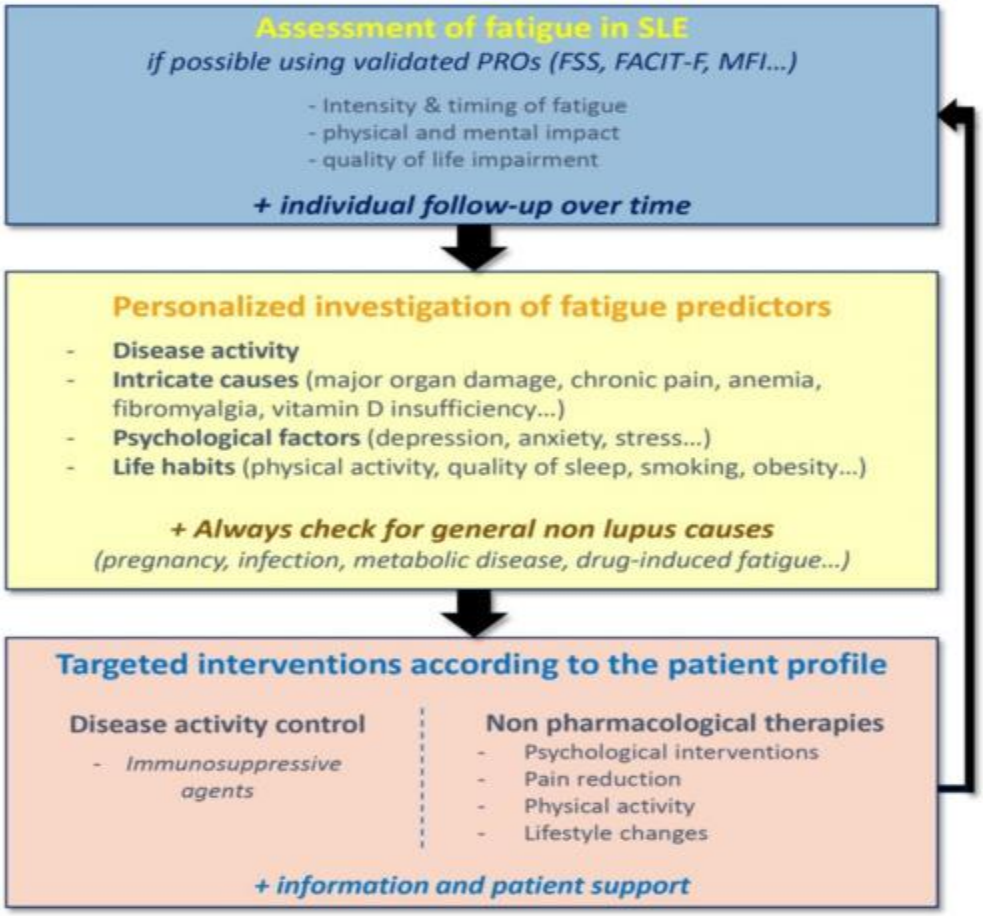

Figure 1. Personalized strategy for the assessment of fatigue in Systemic Lupus Erythematosus. FSS: Fatigue Severity Scale; FACIT-F: Functional Assessment of Chronic Illness Therapy—Fatigue; MFI: Multidimensional Fatigue Inventory **(23).**

A personalized investigation of fatigue predictors is needed, with evaluation of disease activity, search for intricate causes (major organ damage, chronic pain, anemia…) and psychosocial factors, assessment of life habits (physical activity, quality of sleep, smoking, obesity…). Common medical causes of fatigue, such as pregnancy, infections, metabolic diseases or drug-induced fatigue must not be forgotten. Finally, optimal management of fatigue for patients with SLE should be based on providing targeted interventions, according to the patient profile (***25).***

Multiple instruments for assessing fatigue and various definitions are available, without one standing out for its simplicity and reliability. Thus, fatigue is difficult to evaluate in daily practice and to standardize across studies for research purposes.

Fatigue Assessment Scale (FAS)

The Fatigue Assessment Scale (FAS) is a simple 10-item self-reported questionnaire designed by Michielson et al. to assess fatigue in the general population and validated subsequently in the sarcoidosis setting (**26).**

The FAS is reportedly a unidimensional scale measuring fatigue independently from depression. It has proven to be a reliable and valid tool as well as sensitive to change in sarcoidosis patients. Owing to its good psychometric properties in this specific disease, this instrument was then used in a placebo-controlled randomized clinical trial evaluating the effect of *N*-acetylcysteine on fatigue in SLE (**27).**

The FACIT-Fatigue instrument

The FACIT-Fatigue instrument asks patients to rate their experience of fatigue over the prior seven days. The minimal clinically important difference (MCID) in the FACIT-Fatigue scale was evaluated in patients with SLE along with six other fatigue instruments including the Fatigue Severity Scale and the short form-36 (SF-36). In this analysis, the minimal clinically important difference for FACIT-Fatigue score was determined to be an increase of 5.9 points. The FACIT-Fatigue score as well as all of the fatigue scales in this analysis showed significant correlation with the patient self-reported disease activity as measured by the Systemic Lupus Activity Questionnaire and Patient Global Assessment. However, it has long been established that patients and physicians rate disease activity in SLE differently **(28).**

The FACIT-Fatigue scale is a 13-item questionnaire (originally developed in cancer patients) that measures aspects of physical and mental fatigue and their effects on daily living and functioning. The first validation study of FACIT-Fatigue scale in SLE was published in 2011. Like FSS, the FACIT-Fatigue scale has been shown to have good psychometric properties and is easy and quick to administer (< 5 min). Interestingly, all studies that used the FACIT-Fatigue scale found clinically significant associations (**29).**

Fatigue Severity Scale (FSS)

Krupp's FSS was the instrument recommended for use by the 2007 Ad Hoc Committee. It was designed to measure the effect of fatigue on functional outcomes such as exercise, motivation, and daily activities. It has been validated for use in SLE (**30).**

Fatigue was the most frequently cited symptom in the interviews and generated a variety of codes. From these, our concept-based approach identified three general domains of fatigue experienced in SLE: (i) physical manifestation and physical symptoms (including physical energy, endurance, and impact on movement); (ii) mental and cognitive manifestation (including mental energy, motivation and symptoms of cognitive functioning); and (iii) susceptibility to fatigue, or the ease with which patients tire, that is, how easily they tire and how easily their fatigue is relieved (including a rapid, disproportionate and/or unpredictable onset of fatigue). and need for more sleep/rest breaks). In each of them, participants described the severity, variation, and impact of fatigue on everyday life. Participants also described how the experience of SLE fatigue differed from "everyday fatigue" **(31)**.

The FACIT-Fatigue scale and FSS have good construct validity. Both scales have an MCID calculated for patients with SLE, which allows them to demonstrate changes in fatigue that are both statistically and clinically (in terms of MCID) significant. FACIT-Fatigue scale has been reported to have superior internal consistency and greater sensitivity to change than FSS. FACIT-Fatigue scale may be more sensitive to detect subjectively important changes in fatigue levels and potentially able to detect a change in smaller sample sizes. Using focus groups, the FACIT-Fatigue scale has been

shown to have good content validity, which means that it appears to be relevant and sufficient for properly assessing fatigue in patients with SLE **(28).**

Fatigue remains an important issue in patients with SLE. The VAS, though easy to use and often used in long term observational studies, has not been validated in SLE and does not record fatigue's functional effect on patients (**32).**

Multidimensional Assessment of Fatigue (MAF)

The MAF scale is a good choice when selecting an instrument to measure fatigue in chronic illness because it is easy to administer and score; is relatively short in length (it takes less than five minutes to complete); and assesses the subjective aspects of fatigue including degree, severity, distress, impact, and timing. The questionnaire allows patients to omit activity items that do not apply to them, thus making it a more accurate assessment of the impact of fatigue on activities of daily living (ADLs) **(13)**

Multidimensional Fatigue Inventory (MFI)

MFI was developed to meet the need for a questionnaire that excludes somatic items (such as headaches) and measures multiple dimensions of fatigue. It is a 20-item self-report questionnaire with five subscales (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) and has been widely used in numerous studies as a research instrument for a variety of diseases. Although it has been validated in many countries, its construction validity remains under question and there are serious concerns about cultural adaptations of the scale **(33).**

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