

Fatigue in systemic lupus erythematosus

Systemic lupus erythematosus is a chronic inflammatory autoimmune disease often characterized by fatigue, with significant effects on physical functioning and wellbeing. The definition, prevalence and factors associated with fatigue, including physical activity, obesity, sleep, depression, anxiety, mood, cognitive dysfunction, vitamin D deficiency/insufficiency, pain, effects of medications and comorbidities, as well as potential therapeutic options of fatigue in the systemic lupus erythematosus population are reviewed. Due to variability in the reliability and validity of various fatigue measures used in clinical studies, clinical trial data have been challenging to interpret. Further investigation into the relationships between these risk factors and fatigue, and improved measures of fatigue, may lead to an improvement in the management of this chronic inflammatory disease.

KEYWORDS: anxiety • depression • fatigue • physical activity • sleep • systemic lupus erythematosus • vitamin D

The prevalence of systemic lupus erythematosus (SLE) in the USA is estimated to be 15–50 per 100,000 population [1]. There is variability in the reliability and validity of various fatigue measures used in clinical studies. There are also inconsistent findings regarding the usefulness of biomarkers and imaging studies as measures of fatigue in SLE that we also discuss. Finally, we present the knowledge gaps where further research is needed to more precisely measure fatigue to facilitate efficacy assessments of the treatments for fatigue.

Overview of SLE

SLE is a chronic inflammatory autoimmune disease with an unknown cause [1]. The disease can affect the nervous system, skin, joints, serous membranes, kidneys, lungs, as well as other organs. Although SLE can occur in males as well as neonates and children, it is more common in females in their 20s and 30s, especially in non-Caucasian populations including the African-American, Hispanic and Asian populations. The etiology of this disease is still unknown with genetic, environmental, immunologic and hormonal factors contributing to disease susceptibility and severity [2–9].

The American College of Rheumatology's revised classification criteria, published in 1997, for inclusion in SLE research studies, is used to classify eligible patients with SLE if they have four out of 11 clinical and laboratory criteria. There is an ongoing effort to update the 1997 criteria to incorporate new knowledge

regarding clinical and laboratory manifestations of SLE [10].

Patients with SLE have heterogeneous clinical features including complaints of fever, malaise, weight loss, fatigue and photosensitivity. Documentation on physical examination often shows nasal or oral ulcers, alopecia, skin lesions, including malar or discoid skin lesions, joint pain and swelling, pericarditis or pleuritis, or lymphadenopathy. The patients may also have laboratory abnormalities not attributed to other causes such as leukopenia, lymphopenia, thrombocytopenia, elevated creatinine, proteinuria or positive autoantibodies. Severely affected patients may have neurologic sequela such as seizures or psychosis, or renal failure requiring renal replacement therapy with hemodialysis or peritoneal dialysis or renal transplant.

SLE & fatigue

Although there is no clear consensus on a definition for fatigue, Piper has defined fatigue as “an uncommon, abnormal or extreme whole bodily tiredness disproportionate or unrelated to activity or exertion” [11]. Studies have shown that 53–80% of SLE patients have identified fatigue as one of their primary symptoms [11]. When fatigue severity was rated, the scores were similar to previous observations in patients with other chronic illnesses, such as Lyme disease and multiple sclerosis, and higher than the general population [12,13]. One of the major causes of morbidity in SLE patients is chronic, debilitating fatigue [14], decreasing quality of life [15–17], increasing risk of

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work disability [18] with associated cumbersome healthcare costs [19].

Etiology of fatigue in SLE

The etiology of fatigue in the SLE population is multifactorial and is associated with physical activity, obesity, sleep quality, depression, anxiety, mood, cognitive dysfunction, vitamin D deficiency/insufficiency, comorbidities such as fibromyalgia, or related to the SLE disease itself or the treatments used to manage SLE.

■ Physical activity & fatigue in SLE

Previous studies of patients with SLE have shown the impact of aerobic or muscle strengthening or supervised exercise strategies on improved health outcomes including fatigue [20,21], improved exercise tolerance [21–23] and quality of life [22,24]. When aerobic capacity is measured in the physiology laboratory, even patients with mild SLE struggle with performing daily activities and their performance is comparable to levels in individuals with severe cardiopulmonary and metabolic disease [25–27]. SLE patients were found to be less fit with reduced levels of aerobic fitness and reduced exercise capacity including reduced muscle strength, reduced resting lung function, depressed mood, poor sleep quality and functional incapacity, and this physical disability correlated with increased levels of fatigue by a linear regression model [24]. In one study of women with SLE that measured aerobic capacity (maximal oxygen uptake/ VO_2 max) with a bicycle ergometer exercise test during low-to-moderate activity, VO_2 max was significantly lower in SLE females than levels predicted for sedentary women [28]. Another study looking at SLE women and aerobic capacity supported the previous study's findings that aerobic capacity measured by peak oxygen consumption during the treadmill tests was decreased in SLE women compared to controls, was lower than expected for physiologic deconditioning and that this aerobic insufficiency was highly correlated with the perception of severe, activity-limiting fatigue in this population [26].

The list of potential ramifications of low physical activity on health outcomes in SLE was recently extended to include an increased risk of cardiovascular disease as measured by increased proinflammatory biomarkers (e.g., proinflammatory high density lipoprotein [HDL]), the presence of carotid plaques [29–31] and other adverse health outcomes [32].

Mancuso and colleagues compared physical activity levels with clinical and psychosocial

variables including fatigue, depression, social support and stress in 50 patients with SLE. Patients who described more stress and fatigue also reported less physical activity [32]. Only 14 out of 50 (28%) patients met the US government public health goal for the general population of at least 150 min/week of moderate-to-vigorous intensity physical activity. Although 92% of SLE patients believed that physical activity was beneficial for SLE and that they could be more physically active, over 78% believed that SLE impeded their ability to exercise. Patients expressed fears about getting injured during exercise, but they thought physical activity would be beneficial if it were managed appropriately. Fatigue, exposure to sunlight, joint pain, hematologic and bony abnormalities predisposing patients to bleeding and fracture were among the patient-reported physical activity barriers cited to be specific to SLE [32].

■ Obesity & fatigue in SLE

The prevalence of obesity in SLE is between 28 and 50% [33–35]. Few studies have documented associations between diet and nutrient density with SLE and/or fatigue, although adverse associations between obesity and fibromyalgia, functional capacity based on the difficulty performing activities of daily living and inflammatory markers have been noted in SLE [36–38]. Data from LUMINA, a multiethnic SLE cohort study, showed that 28% of the patients were obese, with a BMI of 30 kg/m^2 and above, and that this was associated with worse depression and fatigue [36]. Another study showed a prevalence of obesity of 39% and demonstrated a positive association between obesity and higher levels of fatigue in the SLE cohort [37]. Obesity and SLE are both inflammatory diseases with evidence of increased TNF- α levels in SLE and evidence of increased C-reactive protein and IL-6 levels [39–42]. Higher concentrations of both C-reactive protein and IL-6 increase concerns that these patients may be at higher risk of developing vascular disease. Identifying obesity as a cause of fatigue and poor quality of life in SLE is important, because this risk factor can potentially be modified.

■ Sleep & fatigue in SLE

Sleep disturbances in patients with SLE are common and prevalence can be as high as 91.5% [43–46]. In chronic inflammatory diseases including SLE, sleep-wake disturbances are thought to worsen the disease symptoms including fatigue and lower the patient's quality of life. The pathogenesis behind sleep disturbances are

thought to be the result of pain, stress or depression from the disease itself; either owing to the medications used for treatment, or owing to immune changes from the disease [47]. Patients with SLE report poor sleep quality including frequent awakenings and restlessness. Self-reported questionnaires were used to assess levels of fatigue in 48 SLE female patients in comparison to 27 controls. SLE patients had greater fatigue compared to controls, with reports of longer sleep latency and total sleep time without a higher prevalence of depression [48]. Iaboni *et al.* conducted a study using a polysomnogram showing patterns of low sleep efficiency (defined as total sleep time during time in bed attempting to sleep), deficits in slow-wave sleep, high frequency of arousals during sleep and high levels of α -EEG sleep activity in SLE patients compared to healthy controls, which was comparable to the pattern of unrestorative sleep found in patients with fibromyalgia. However, there was no significant association between sleep and clinical features of SLE disease or disease activity. Mild-to-moderate depression was found among the study population, but they found that sleepiness in SLE patients was not associated with depression. SLE patients with severe depression complained mostly of tiredness but were not always objectively sleepy. The authors concluded that primary sleep disorders are common among SLE patients and are related to their fatigue, but distinct from depression contributing to fatigue [49].

Other studies supported the finding of increased unrestorative sleep in SLE patients by showing high frequency of primary sleep disorders including sleep apnea and abnormal limb movements during sleep in SLE patients, as well as increased daytime sleepiness due to sleep fragmentation and more arousals [50,51]. One study assessed 100 women with SLE and their sleep quality by utilizing the Pittsburgh Sleep Quality Index [52], a questionnaire that assesses sleep quality and disturbances over a 1-month period. Completed questionnaires reflected moderate-to-severe sleep impairments in 56% of the SLE population. Cumulative damage, disease activity, functional disability, pain severity, use of prednisone, depressed mood and lower levels of exercise participation were all positively correlated with poorer sleep quality [46].

■ Depression, anxiety, mood, cognitive dysfunction & fatigue in SLE

The prevalence of depression and anxiety in SLE is as high as 28 and 24%, respectively [53].

Depression has been consistently associated with fatigue in SLE patients [13,17,24,45,48,54–56]. In a study by Krupp *et al.*, the degree of depression among patients with SLE was measured by the Center for Epidemiologic Studies Depression scale [56], a 20 item validated inventory (higher scores suggest a higher risk of depression) [57]. The scores of SLE patients were higher than the normal population but milder when compared to psychiatric patients, and similar to those with other chronic medical conditions. However, the correlation between fatigue scoring and depression was higher in the SLE population than other medical conditions such as Lyme disease or multiple sclerosis [12,36,56].

Anxiety and mood disorders have been implicated as one of the contributing factors of fatigue in SLE [48,56]. Tench *et al.* used questionnaires to measure self-reported fatigue, disease activity, sleep quality, quality of life, anxiety and depression in 120 SLE patients [45]. Anxiety and depression were measured using the Hospital Anxiety and Depression scale (HAD) [58], which is used to assess mood in patients with physical disease. A HAD score of eight or above suggests a possible mood disorder and ten or above suggests a pathological mood disorder. Approximately one third of these patients had HAD scores suggestive of a pathological mood disorder, and in contrast approximately 13% were taking antidepressant medications. The authors concluded that since a moderate correlation was seen between HAD depression scores and fatigue, depression and anxiety may contribute to SLE fatigue [45].

Little is known about the pathology behind cognitive dysfunction associated with fatigue in the SLE population, although cognitive impairment has been one of the main complaints in patients with SLE compared to controls [59]. Prevalence of cognitive dysfunction in SLE patients ranges from 27 to 61%, with deficits shown in learning or memory, reasoning, fluency and attention, as well as processing speed deficits [60–62]. Kozora *et al.* examined neuropsychological and neurologic functioning in 67 SLE patients without histories of overt neuropsychiatric disorders compared to 29 healthy controls. Results showed that SLE patients had significantly higher rates of impairment on logical reasoning and verbal memory, and trends towards greater impairment in visual attention and working memory [63]. These patients also had higher depressive symptoms and perceived cognitive difficulties compared with controls on the Beck Depression Inventory [64] and the Cognitive Failures Questionnaire [65], respectively.

■ Vitamin D & fatigue in SLE

Vitamin D plays a crucial role in bone metabolism and bone health [66,67], with recent studies suggesting vitamin D deficiency playing an important role in cardiovascular disease, cancer and autoimmune diseases. Vitamin D deficiency has been related to higher risk of cardiovascular disease, increased risk in all-cause mortality in the general population, as well as increased risk of autoimmune diseases including SLE [66,68,69]. Although the role of vitamin D in the pathogenesis and clinical course of SLE are largely unknown, suboptimal levels of vitamin D have been reported in the SLE population [70–72]. A relationship between fatigue and vitamin D insufficiency, defined as serum levels of 25-hydroxyvitamin D (25[OH]D) below 30 ng/ml, and deficiency, defined as serum levels of 25(OH)D below 10 ng/ml, were found in a study by Ruiz-Irastorza *et al.* Among 92 patients with SLE, 75% presented with vitamin D insufficiency and 15% with vitamin D deficiency. The high prevalence of vitamin D insufficiency and deficiency in the SLE population is multifactorial and is exacerbated by specific issues related to SLE such as the recommendation to avoid sun exposure because of the risk of increased disease activity from photosensitivity. SLE patients with vitamin D deficiency had a higher degree of fatigue on the 0–10 visual analog scale (VAS) with a mean score of 5.32 compared to 4.03 in patients with 25(OH)D levels above 10 ng/ml ($p = 0.08$). The authors concluded that critically low 25(OH)D levels below 10 ng/ml was an independent predictor of higher values of VAS used to measure fatigue, and suggested checking vitamin D levels in SLE patients experiencing tiredness [73]. In an observational study by the same author where oral vitamin D3 was supplemented for low 25(OH)D levels in SLE patients, fatigue quantified by VAS improved in the cohort members who used the oral supplements. They also found an inverse association between 25(OH)D levels and the VAS score [74].

■ Pain & fatigue in SLE

Pain related to arthralgias and arthritis can occur in up to 95% of SLE patients during the course of their disease [75]. Zonana-Nacach *et al.* found that pain among other psychosocial cofactors does contribute to higher levels of fatigue in these patients [76]. In this study, patients subjectively estimated their pain attributable to SLE with 0–10 VAS, and fatigue was measured with the Fatigue Severity Scale (FSS) [77]. During their analysis, a significant positive association

was found between levels of fatigue and self-reported pain attributed to SLE among other variables [76]. Jump *et al.* studied correlations between pain, psychological distress and their association with fatigue in SLE patients. One hundred and twenty-seven participants completed questionnaires for fatigue, disease activity, pain and depression. As predicted, fatigue was the most highly rated symptom compared to other complaints, with higher scores seen on VAS for pain. When they conducted a correlational analysis, fatigue was moderately associated with pain intensity ($r = 0.43$; $p < 0.001$) and depression ($r = 0.48$; $p < 0.001$) [78].

■ Medication & fatigue in SLE

Reports suggest that medications used to treat SLE may themselves be associated with fatigue. One study showed that fatigue scores did not differ significantly between SLE patients taking corticosteroids and those who were not taking corticosteroids, but patients taking NSAIDs reported significantly higher fatigue scores compared to those who were not. Pain scores were reported to be higher among those patients taking NSAIDs, but when corrected for pain as a contributing factor for the fatigue scoring, the difference was no longer apparent. Also the use of psychotropic medications such as antidepressants or anxiolytics did not make a significant difference on the reporting of subjective fatigue between those taking and those not taking these medications [78].

■ Comorbidities & fatigue in SLE

Fibromyalgia can be seen from as low as 10% to as high as 70% in study populations coexisting with SLE [49]. Fibromyalgia coexisting with SLE has been thought to contribute to fatigue in SLE patients [78]. One study showed a prevalence of fibromyalgia in only 10% of 216 SLE patients complaining of fatigue [50], but another study showed higher prevalence of fatigue in SLE patients with a pain syndrome although these patients did not fit the American College of Rheumatology's criteria for fibromyalgia [79]. Since fibromyalgia may coexist with SLE-diagnosed patients, comorbidities other than SLE itself causing fatigue in this patient population should be considered. Thyroid disease and anemia have also been implicated as affecting fatigue in SLE patients [14].

■ Disease activity & fatigue in SLE

One would suspect that having SLE, a chronic disease, itself would contribute to fatigue, but

findings have been more conflicting, with some showing significant positive association [13,80,81], and others with weak or no association [45,56,76,78,79,82–85]. Wang *et al.* studied the relationship between fatigue and disease activity in the SLE population using the Systemic Lupus Erythematosus Disease Activity Index and fatigue using the FSS. No significant correlation between FSS and Systemic Lupus Erythematosus Disease Activity Index were found, and they concluded that fatigue in SLE patients does not correlate with disease activity [84]. Another study demonstrated that fatigue symptoms do not correlate well with any of the laboratory measures, but physician's rating of disease activity correlated well with patient's fatigue [56]. Tayer *et al.* investigated the contributions of disease status, feeling of helplessness and depression to fatigue in SLE patients. Eighty one SLE patients underwent clinical evaluation with the Systemic Lupus Activity Measure and completed self-reported questionnaires on psychosocial data, depression, feelings of helplessness and fatigue. The authors concluded that SLE disease status predicted fatigue at two different time points in the longitudinal analysis, independent of depression and helplessness, by using hierarchical multiple regression analyses [80].

Measurements of fatigue

■ Survey instruments

Although fatigue can only be measured subjectively, the impact of fatigue on quality of life is still important. There have been inconsistent definitions for fatigue used in clinical studies utilizing different instruments to measure fatigue. At least 30 different scales are available to test fatigue in general. Owing to the inconsistencies, an *Ad Hoc* Committee on SLE response criteria systematically reviewed the literature on validated instruments on fatigue used in SLE. Fifteen different fatigue instruments were reviewed focusing on validity, reliability and responsiveness, as well as correlations between fatigue and cofactors, such as disease activity, depression, pain and sleep. The instruments surveyed included the FSS, Chalder Fatigue Scale [86], Robert B. Brigham Multipurpose Arthritis Center-Fatigue Scale [23], Piper Fatigue Scale [87], Short Form of the Medical Outcome Study questionnaire plus one item for fatigue [88], Fatigue Self-Efficacy Scale (FSES) [89], Short Form-36 vitality subscale [90], Multidimensional Assessment of Fatigue [91], Multidimensional Fatigue Inventory 20 items [92], fatigue rating [81], VAS [93], Fatigue Assessment Instrument

FAI [94], VAS-fatigue [95], Sjogren's-Based Psychometric Instrument [96] and single question for fatigue [50]. Among the 34 SLE studies that used these 15 instruments, the FSS was most commonly used and thought to have a homogeneous pattern in measuring outcomes when applied to studies, making it a clinically important scale to be used in future studies. The panel concluded that this instrument was developed specifically for patients with SLE and had valid psychometric properties including internal consistency, responsiveness and construct validity. They proposed that an improvement or response of $\leq 15\%$ decrease in the FSS was considered clinically important but called for future studies to test this recommendation [77].

■ Biomarkers

Possible correlations between serum biomarkers for inflammation in SLE and fatigue were evaluated in a cross-sectional study. Some changes in cytokine levels have been observed in SLE, with shifts towards Type 2 cytokines such as IL-2, IL-6, IL-10, TNF- α and INF- α [97–99]. In chronic fatigue syndrome patients, increased levels of TGF- β , TNF- α , IL-2 and IL-6 with other cytokines are seen [100–102]. These studies concluded that these cytokines do play a role in fatigue, with profound fatigue after infusion of these cytokines and immediate improvement in fatigue following anti-IL-6-receptor antibody therapy [103–106]. Omdal *et al.* studied SLE patients to determine whether fatigue was associated with levels of serum cytokines including TNF- α , IL-2, IL-6, IL-10, TGF- β , IFN- α , antiphospholipid antibodies including anticardiolipin antibody and $\beta 2$ -glycoprotein I antibody, as well as changes seen in cerebral MRI. Among 57 patients, 45 (79%) reported fatigue on FSS and nine (17%) had cerebral infarcts on MRI, although no differences in FSS scores were observed between patients with or without infarcts on MRI. No particular associations were seen between FSS and anticardiolipin antibodies, $\beta 2$ -glycoprotein I antibodies, TNF- α , IL-2, IL-6, IL-10, TGF- β and IFN- α , and the authors concluded that SLE markers of disease or inflammation, evaluated by serum cytokine levels and brain imaging, did not influence fatigue [83]. In the same study, the authors found that low levels of C4 were the only biomarker that correlated with fatigue.

■ Imaging

There have been inconsistent findings correlating the association of levels of fatigue to changes of

brain imaging. The study by Omdal *et al.* did not find a significant association between infarcts seen on MRI to fatigue in SLE patients [83]. In another study by Harboe *et al.*, utilizing a semi-quantitative radiologic scale on a T2-weighted MRI study, noted that cerebral white matter hyperintensities (WMH), previously associated with cognitive impairment in multiple sclerosis, were also present in SLE patients [107]. The WMH changes are known to represent biochemical changes in brain tissue frequently seen in patients with SLE [80]. Among 62 SLE patients, fatigue scores measured by FSS and VAS were higher among SLE population (FSS 4.3 with SD 1.7 and VAS 48.9 with SD 30.1) compared to healthy subjects (FSS 2.3 with SD 1.0 and VAS 19.7 with SD 19.7). Eleven (18%) SLE patients had cerebral infarcts compared to two (3%) healthy subjects, and total WMH scores were higher in SLE patients compared to healthy subjects. Only fatigue measured by VAS, not FSS, correlated with total WMH score. The authors concluded that fatigue is associated with a higher cerebral WMH load in SLE patients, supporting evidence for the biological explanation for fatigue in patients with chronic autoimmune diseases [107]. Another study utilized single-photon emission computed tomography imaging to investigate whether disturbances of cerebral blood flow (CBF) can be seen in SLE patients with fatigue. Single-photon emission computed tomography resulted in focal CBF disturbance in 17 out of 57 (30%) patients and generalized CBF reductions in 32 out of 57 (57%) patients, although no significant association between CBF and degree of fatigue was seen. They concluded that there was no association between fatigue in SLE patients and disturbances of brain blood perfusion pattern [108].

Treatment of fatigue

Fatigue is a frequent and pervasive problem with multiple adverse consequences for patients with SLE, but to date there have only been a few clinical trials that have addressed the pharmacologic and nonpharmacologic management of fatigue in SLE populations.

Psychoeducational intervention has been used in trials compared to placebo, with reported improvement in social support between patients and their partners, better self-efficacy and lower fatigue after 1 year of therapy, calling for a role of behavioral therapy in the management of fatigue in SLE [109,110].

A pilot study to investigate the feasibility and safety of acupuncture for SLE explored the

benefits of acupuncture in reducing pain and fatigue. Twenty four patients were randomized to receive acupuncture with electrical stimulation, minimal needling, which involves shallow insertion of needles into nonacupuncture body points, or usual care during ten sessions. No serious side effects occurred, although some minor transient side effects were reported, mainly needle insertion pain, dizziness or lightheadedness, or local bruising. A total of 40% of patients receiving active intervention with acupuncture or minimal needling reported more than a 30% improvement in pain scores measured by the Arthritis Impact Measurement Scale revised Pain Scale or the 36-item Short-Form Health Survey bodily pain scale [111–113]. Only 13% in the minimal needling group, but 25% in the acupuncture group showed improvement in fatigue, measured with FSS or 36-item Short-Form Health Survey vitality score, suggesting that a brief course of acupuncture may be a useful nonpharmacologic alternative for managing pain and fatigue for SLE patients [114].

A recent pilot study evaluated the effectiveness of home-based exercise programs using the Wii Fit® system in SLE patients. Fifteen patients who had moderate-to-severe fatigue measured by FSS participated in Wii Fit®, a fitness gaming module, 3 days a week for 30 min each time. Even though the mean adherence was 64% across the 10-week period, patients' perceived fatigue severity significantly improved by average of 18.4%, with added benefits of reduced body weight and waist circumference. Other improvements were seen including reduced anxiety level and pain, and the authors concluded that this method was safe and feasible and may be a viable option to encourage physical activity and reduce fatigue, body weight, waist circumference, anxiety and overall intensity of pain [115].

Hartkamp *et al.* investigated the role of dehydroepiandrosterone (DHEA) in improving fatigue and reduced wellbeing in patients with SLE in a randomized placebo-controlled trial of 60 patients [116]. Patients with SLE have frequently been found to have low levels of DHEA, which is a major steroidal product in the adrenal gland. Previous research studies observed a relationship between physiologic decline in serum DHEA and DHEA sulfate levels during aging with atherosclerosis, global changes in metabolism, decline in cerebral function and immunocompetence, potentially linking the DHEA to rheumatic diseases [117]. DHEA has shown some beneficial effects when administered in older patients and

in patients with other disease states including cardiovascular disease [117]. This study was conducted in patients with quiescent SLE to avoid other confounding factors, with daily oral administration of 200 mg DHEA. Fatigue was measured using the Multidimensional Fatigue Inventory [92], with both placebo and DHEA groups improving on fatigue scores with no proven benefit of DHEA over placebo in improving fatigue [116].

A recent randomized, double-blind, placebo-controlled clinical trial of a newly approved B-lymphocyte stimulator, belimumab, has assessed fatigue as a secondary end point using the Functional Assessment of Chronic Illness Therapy Fatigue scale [118], and 52-week and 76-week studies showed a significant improvement in fatigue compared to placebo [119,120].

Future perspective

Fatigue is a primary complaint of patients with SLE. One critical research need is to improve the measurement of fatigue for use in clinical trials. One potential tool, Patient-Reported Outcomes Measurement Information System, uses rigorous instrument-development standards and item response theories to create questionnaires that

can be used across different clinical trials and varied disease conditions [95]. Improved unified fatigue measurements will facilitate further studies of fatigue and help guide therapy.

There is a constant interplay between different cofactors that may contribute to fatigue experienced by SLE populations, including poor sleep, depression, anxiety, mood disorders, physical inactivity, obesity, vitamin D insufficiency/deficiency, the disease itself, or other confounding comorbidities. Nonpharmacologic and pharmacologic interventions have been minimally to moderately effective in ameliorating fatigue and further investigations in these areas are needed.

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Executive summary

Systemic lupus erythematosus & fatigue

- A total of 53–80% of systemic lupus erythematosus (SLE) patients identify fatigue as one of their primary symptoms. Fatigue results in decreased quality of life, increased risk of work disability and increased healthcare costs.

Factors associated with fatigue

- SLE patients' aerobic capacity is often decreased compared to healthy controls and studies have shown improved health outcomes including decreased fatigue from increasing physical activity.
- Obesity is prevalent in the SLE population, with a BMI above 30 kg/m² associated with worse depression and fatigue.
- A bidirectional relationship exists between fatigue and poor sleep, with SLE cohorts usually experiencing more sleep–wake disturbances and unrestorative sleep.
- Depression has been consistently associated with fatigue and anxiety and mood disorders have been correlated with fatigue in SLE patients compared to healthy controls.
- Suboptimal levels of vitamin D have been reported in the SLE population, with vitamin D deficiency correlating with worse fatigue.
- There is a positive correlation between pain intensity and fatigue in the SLE population.
- No significant associations were found between corticosteroids or NSAID use and fatigue severity.
- Coexisting fibromyalgia, thyroid disease and anemia may also affect fatigue in SLE.
- Conflicting theories exist, with one side showing positive correlation between SLE disease activity and fatigue, and the other arguing for weak or no association.

Measurements of fatigue

- Over 30 scales exist to test fatigue as a research tool.
- Various serum biomarkers for inflammation have been evaluated for their association with fatigue in SLE, including antiphospholipid antibodies, transforming growth factor- β , TNF- α , IL-2, IL-6 and IL-10, with few studies showing positive correlations.
- There have been inconsistent findings correlating the association of levels of fatigue to changes of brain imaging using different modalities including MRI and single-photon emission computed tomography.

Therapeutic trials

- Different therapies have been studied to improve fatigue in SLE: psychoeducational intervention to increase wellbeing, computer gaming modules to increase physical activity, acupuncture to decrease fatigue and pain and medication trials with dehydroepiandrosterone, belimumab, and vitamin D₃, with some showing positive results.

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