Fatigue in inflammatory rheumatic diseases: Current knowledge and areas for future research

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Abstract

Fatigue is a complex phenomenon and a significant health concern for many people with inflammatory rheumatic diseases, such as rheumatoid arthritis, psoriatic arthritis, primary Sjögren's Syndrome, and systemic lupus erythematosus. Although some trials have shown the benefits of fatigue self-management, the effect is relatively modest and no curative treatment has been identified and the pathogenesis of fatigue remains unclear. Despite many challenges and limitations, there is a growing body of research into the role of the immune system, the central and autonomic nervous system as well as the neuroendocrine system in the induction and maintenance of fatigue in chronic diseases. New insights have also been gained on how sleep, genetic susceptibility, metabolic disturbances, and other biophysiological mechanisms may contribute to fatigue. Furthermore, advances have been made in better understanding of the relationships between various psychosocial factors and fatigue. However, the interrelationship between these diverse mechanisms and fatigue remains poorly defined. In this review, we outline various biophysiological and psychosocial determinants of fatigue in inflammatory rheumatic diseases. We then propose mechanistic and conceptual models of fatigue to summarise current understanding, stimulate debate and support the development of further research ideas.

Introduction

Inflammatory rheumatic diseases (IRD) are a group of multi-system, immune-mediated rheumatic conditions such as Primary Sjögren's Syndrome (pSS), Systemic Lupus Erythematosus (SLE), vasculitis, Psoriatic Arthritis (PsA) and Rheumatoid Arthritis (RA)(1). Although the clinical manifestations of IRD vary, fatigue is often a prevalent and disabling symptom in many IRD(2).

Patients with IRD have identified fatigue as one of the most challenging symptoms to cope with(3) and manage, as well as associated with poor quality of life(4). It is also a highly prevalent experience and an international study of >6,000 patients found that one out of every two was severely fatigued, defined as scoring ≤35 on the SF-36 Vitality Scale(1).

Fatigue is also an important independent predictor of job loss and disability in patients with RA, ankylosing spondylitis, SLE, pSS and vasculitis(5-9). Considering the widespread personal impact of fatigue and its health economic burden, discerning the underlying mechanisms and finding effective treatment are priorities. We have taken a biopsychosocial approach(10), systematically considering biological, physiological, psychological, and social factors and their complex interactions in understanding fatigue mechanisms.

The challenges of fatigue research

Fatigue is a complex, multifaceted phenomenon and there are many challenges in fatigue research which limit our current understanding (Box 1). Conceptually, there is the question of defining fatigue. Most people have experienced fatigue during their everyday life, but qualitative research on fatigue associated with chronic diseases (referred to as "pathological fatigue") suggest that it is different from their "usual" premorbid fatigue experience. The most distinguishing features include perceiving the fatigue to be unearned, a lack of improvement with rest, variability in severity, unpredictability, and fatigue being more profound/overwhelming(11, 12). Patients often explain their fatigue in relation to the extensive impact that it can have on all aspects of their daily lives(13). Such findings suggest that "pathological fatigue" maybe driven by different mechanistic pathways to the "usual" fatigue experienced in healthy individuals, although the mechanisms of both "types" of fatigue remain poorly defined. A related consideration is whether fatigue

associated with different chronic conditions (e.g. RA, fibromyalgia, inflammatory bowel disease, Parkinson Disease, cancers, etc) are similar phenomenon. Studies have shown that the quality of perceived fatigue is similar across different chronic diseases (which included both inflammatory and non-inflammatory conditions)(14, 15). Studies in different diseases have also identified similar "predictors" for fatigue (Box 2). Furthermore, fatigue correlates poorly with disease activity of the underlying conditions. These observations suggest that fatigue may be the same phenomenon across different chronic conditions. Here, we focus our discussion on "pathological fatigue" associated with IRD. For simplicity and readability, the term "fatigue" is used.

Another challenge is how to measure fatigue accurately and reliably. Fatigue is inherently a subjective phenomenon and assessment relies on the use of standardised questionnaires. Many fatigue questionnaires have been developed, and there are several factors to consider when selecting a measure(16). These include generic versus disease-specific, single item versus multi-item, and instruments that provide a single overall score (usually for level/severity of physical fatigue) versus instruments that provide sub-scale scores for different fatigue domains (e.g., physical, cognitive, emotional). The number of questionnaires in use and the lack of an agreed gold standard means that comparisons across studies are difficult(17). Conceptual and psychometric issues include differing recall periods, variation in wording between questionnaires and the lack of defined cut-off value for cases for most of them. Moreover, these questionnaires poorly capture the variability of the fatigue. Finally, patient reported outcomes are prone to recall bias and other psychosocial influences. Objective assessment of fatigue, if available may overcome some of these issues, although we recognise the importance of capturing patients' perceptions alongside to aid interpretation of the outcomes.

Other barriers to fatigue research include how to address potential confounders of fatigue, and the lack of information on pre-morbid fatigue state.

Putative mechanisms implicated in fatigue

"Look and you will find it - what is unsought will go undetected." - *Sophocles (496-406 BC), classical Greek writer*

Many biophysiological and psychosocial mechanisms have been implicated in fatigue pathogenesis (Figure 1). However, the cross-sectional nature of many of the studies makes establishing causality and directionality a challenge. Furthermore, complex interactions exist between many of these mechanisms. Therefore, it is likely that several (if not all) of these mechanisms are in operation with the relative contribution of each mechanism differing between patients and potentially within patients, over time. It is therefore important that support for fatigue is tailored to individuals and involves exploration possible drivers. A systematic review of factors associated with fatigue identified a cluster of variables that should be considered as potential maintaining factors, including psychological and physical functioning, pain, sleep disturbance and depression and anxiety(18).

Due to the vast number of published articles mentioning "fatigue", and the challenges we mentioned in drawing comparisons between different research studies on fatigue, we have not performed a comprehensive, systematic literature search. The findings discussed in this review represent our interpretation of the relevant evidence in the literature. In addition, there have been several excellent recent reviews on the role of inflammation and the brain in fatigue pathogenesis (19-22), we want to use the limited space to include discussion of other potential contributing mechanisms of fatigue that currently do not receive much attention. We hope that this will generate further discussion and debate among the research community, which in turn bring further advance in fatigue research.

Bio-physiological mechanisms

Immunological mechanisms

Inflammation is arguably the most studied mechanism of fatigue. The "sickness behaviour" model in animals and in man have provided not only strong evidence for inflammation-induced fatigue but also revealed potential molecular basis. In this model, fatigue is an adaptive immune-mediated response by vertebrates to enhance survival from infection, with the production of type I interferons and other pro-inflammatory cytokines contribute to sickness behaviour which can include fatigue, anhedonia, social withdrawal and depression(23). Energy expenditure is reserved for the immune system and social withdrawal prevents further disease spread and reduces risk from predators when their health is impaired(24).

There is a large body of data demonstrating the links between inflammation and fatigue in IRD and it is a subject of regular review in the literature (5, 19, 20, 25). However, how far the acute sickness behaviour model and inflammation explain fatigue in chronic IRD remains unclear. This is because if inflammation is the only driver of fatigue, one would expect a strong correlation between fatigue levels and pro-inflammatory cytokines and disease activities, that fatigue should improve with immuno-modulatory treatment and subside when the underlying IRD is in remission. However, although circulating levels of pro-inflammatory cytokines are typically elevated in IRD compared to healthy controls and non-inflammatory rheumatic disease(26, 27), higher circulating levels of these cytokines do not necessarily associate with worse fatigue. Several studies in pSS even revealed an inverse relationship between fatigue severity and circulating levels of pro-inflammatory cytokines (IP-10, TNFα, LTα and IFNγ), and such inverse relationships between these pro-inflammatory cytokines and fatigue, together with depression and pain, were key predictors of fatigue in a multi-regression model(26, 28). Similarly, an inverse relationship between interferon activation and fatigue was observed in pSS(29, 30). In addition, using gene set enrichment analysis of the genome-wide transcriptomic data of 133 pSS patients, 19 biological pathways were found to be associated with fatigue, but none was overtly inflammation-related(31).

In IRD, while fatigue often accompanies disease flare(21), there is no consistent relationship between fatigue and validated disease activity scores (32-37). In particularly, a significant proportion of patients with IRD continue to experience disabling fatigue despite seemingly in clinical and biological remission(37). Conversely, a small proportion of patients do not experience fatigue despite having active disease(29, 36).

Regarding the relationship between fatigue and immuno-modulatory treatments used in IRD, a Cochrane review summarising the interventions for RA with fatigue either as a primary or secondary outcomes has been published (38). A meta-analysis of these studies demonstrated that both anti-TNF biologics and non-anti-TNF biologics led to a statistically significant reduction in fatigue in patients with active RA compared to controls. Most studies in RA utilised TNF-targeting therapies, other therapies include rituximab, tocilizumab, canakinumab, abatacept and anti-IFN-γ with most trials running for 24 weeks or less. The improvement was similar for both anti-TNF and non-anti-TNF therapies. It is, however, unclear as to whether fatigue improvement was a direct result from reduction in disease activity and inflammation, or indirectly via another mechanism such as pain(35). It should be noted that participants in these trials had a high level of disease

activity and fatigue was measured as a secondary outcome and little adjustment was made for confounding factors in the included trials. Furthermore, many RA patients continue to experience disabling fatigue despite no demonstrable synovitis or systemic inflammatory responses(37)(38).

In SLE and pSS, the clinical trial data on the effect of immune-modulating therapies on fatigue were inconsistent. For example, four out of seven trials of rituximab showed a significant reduction in fatigue(39-41), two studies showed a mild improvement only at certain time points(42, 43) and one study showed no effect(44). A phase 2 trial of RSLV-132 (a fusion protein of RNase-IgG) in pSS showed improvement in fatigue. Intriguingly, improvement of fatigue was accompanied by increase in IFN modular scores(30). In SLE, the initial trials of belimumab (BLISS-52 and BLISS-76) measured fatigue as a secondary outcome using SF-36(45, 46). In the post-hoc analysis, significant improvements from baseline were demonstrated in the 10mg/kg group compared to placebo in BLISS-52, but not BLISS-76(47). In a longer trial, regular belimumab treatment over six years led to a reduction in fatigue scores(48). Interestingly, fatigue levels rose initially with belimumab, suggesting that sustained therapy may be needed to see improvement.

Overall, these observations indicate a complex relationship between fatigue and disease activity of the underlying condition, and the relationships between pro-inflammatory responses and fatigue in IRD remain to be fully defined. Inflammation likely plays a key role in initiating fatigue response, particularly at early stages of the disease and during disease flares. However, the evidence for systemic inflammation in the maintenance of fatigue in chronic disease is less clear. In some individuals, it might not be an important factor and additional mechanisms are needed. Consistently, it has been reported that following interferon-α therapy for treatment of hepatitis C, some patients continued to experience fatigue even six months after completing the treatment when interferon-α is no longer present(49).

Arguably, fatigue that is closely correlated to underlying disease activity and/or systemic inflammation is of less clinical and scientific importance, as such fatigue should improve when the underlying disease is treated or when systemic inflammation is suppressed. In contrast, it is fatigue that dissociates with disease activity being the conundrum clinicians, scientists and pharmaceutical industry is facing and represents the largest health economic burden and unmet need to the patients and society.

Central Nervous System (CNS)

Several characteristics of fatigue point to the potential involvement of the CNS. For instance, symptoms such as perceived cognitive impairment and lack of motivation are common among fatigued patients(50). Furthermore, CNS may contribute to muscle fatigue during exercises through reducing the neural drive to the muscles(51).

Korte and Straub have published an excellent review recently on how inflammation may alter neurochemistry and functional connectivity in the brain which in turn may contribute to fatigue(22), which offers an extensive review on this topic. Bidirectional communications between the immune system and the brain are mediated by multiple signalling pathways(23, 52). Circulating pro-inflammatory cytokines may lead to microglia activation in the brain(53). This could be achieved through direct transfer of cytokines across the blood brain barrier via various mechanisms (receptor-mediated transcytosis, leakage across damaged tight junction or circumventricular organ), or indirectly via other pathways, such as activated vascular endothelial cells or the vagus nerve (Figure 2A). Pro-inflammatory activities in the brain in turn results in several changes. Firstly, the release of the neurotransmitter noradrenaline, which is important for increasing arousal, alertness and attention, is inhibited. Secondly, the uptake and breakdown of monoamines (serotonin, dopamine and noradrenaline) is increased, reducing their availability in the synaptic cleft(22). Thirdly, tryptophan-2,3-dioxygenase and indoleamine-2,3-dioxygenase (IDO) which promote tryptophan (TRP) into the kynurenine (KYN) metabolic pathway, is increased. The metabolites of the KYN pathway further induce local inflammation in the brain. In a rat model where central fatigue was induced, metabolites of the KYN pathways were found in presynaptic neurons of the hypothalamus, hippocampus, and cerebral cortex(54). In SLE and RA, KYN pathway activation and elevated KYN/TRP ratios have been reported and correlated with fatigue(55, 56). However, in another study, peripheral levels of IDO-1 mRNA levels were similar between fatigued and non-fatigued PSS patients(57). TRP also acts as a precursor for serotonin synthesis. Therefore, TRP depletion may result in decrease in serotonin, which play a key role in mood and cognitive functioning. However, in SLE, TRP metabolism correlated with fatigue but not depression(55). Increased plasma KYN levels were associated with exhaustion of athletes and correlated with worse fatigue and depression scores in haemodialysis patients(58, 59). However, in a study of hepatitis C patients receiving IFN-α treatment, although altered levels of KYN metabolites were observed, they were not associated with persistent fatigue(49).

Direct evidence of pro-inflammatory or metabolic changes in the CNS in fatigued patients however remains elusive. Larssen and co-workers performed proteomic (LC-MS/MS) analysis of cerebrospinal fluid (CSF) from fatigued and non-fatigued pSS patients and identified 15 discriminatory proteins but none have known pro-inflammatory function(60). Instead, many were associated with cellular stress responses, cellular metabolism and depression. However, in another study of pSS patients focussing on the role of IL-1 pathway, CSF level of IL-1R antagonist (IL-1RA), a natural inhibitor of IL-1β, was elevated and predicted severity of fatigue (alongside depression and pain)(61, 62). The finding could reflect IL-1β pathway activation in the CNS.

Neuroimaging is a promising tool for exploring the role of the CNS in fatigue. Magnetic Resonance Imaging (MRI) may show volume changes in different areas of the brain, and functional MRI (fMRI) may reveal alterations in neural network during fatiguing tasks. For instance, Schrepf et al have identified significant correlation between fatigue and specific changes in neuro-connectivities in RA(63). In another fMRI study, Basu et al have reported fatigued patients with Granulomatous Polyangiitis (GPA) showed hyperactivity in several regions during a mental challenge task(64). In a meta-analysis of fMRI and positron emission tomography (PET) studies that involves either markers of peripheral inflammation or induced inflammation have identified brain regions and networks that are associated with peripheral inflammation in man(65). Some of these brain regions and networks could provide an explanation of the sickness behaviour. However, this mata-analysis did not directly explore the relationship between the CNS changes and fatigue. In another systematic review of MRI studies of fatigue in chronic diseases, the brain areas implicated in fatigue were highly heterogeneous not only between different conditions, but also in different studies in the same disease(66). Similarly, a systematic review found conflicting data regarding lesion location and post-stroke fatigue(67). Thus, more research is needed to characterise the relevant CNS changes in fatigue.

Neuroendocrine disturbance

An appropriate cortisol response is important for the body to handle stressors which can be physical (e.g. injuries), physiological (e.g. hypotension), pathological (e.g. infections) or emotional (e.g. significant life events). Cortisol production is primarily regulated by the HPA axis. There is a complex interaction between the HPA axis and the immune system. Pro-inflammatory cytokines (particularly the gp130 family cytokines (e.g. IL-

1, IL-6)) stimulate corticotropin-releasing hormone (CRH) production by the hypothalamus and adrenocorticotropic hormone (ACTH) production by the pituitary glands(68), resulting in increased cortisol production by the adrenal glands. Cortisol in turn suppresses pro-inflammatory responses, completing a feedback loop (Figure 2B). With persistent inflammation, however, the response of the HPA axis could be blunted(69).

In addition to immune-modulatory effect, cortisol plays a major role in the regulation of metabolism. Cortisol and other glucocorticoid hormones increase the availability of energy source by mobilising the release of glucose, free fatty acids, and amino acids from endogenous stores.

Fatigue and lack of motivation are well-recognised features of hypoadrenalism. In clinical studies, HPA dysfunction may be demonstrated by reduced basal cortisol levels, relative cortisol insufficiency (e.g. reduced cortisol/pro-inflammatory cytokine ratio) or "suboptimal" cortisol response to stimulation (e.g. exogenous ACTH/CRH or hypoglycaemia states). Blunted HPA axis has been reported in pSS(70), RA(71, 72) and SLE (73) patients compared to healthy controls.

However, few studies have directly explored the link between HPA axis dysfunction and fatigue in IRD. Evers et al conducted a longitudinal study exploring the relationships between daily stressors, worrying, HPA axis (cortisol), pro-inflammatory cytokines, disease activity, pain and fatigue over 6 months in 80 RA patients. They showed that daily stressors, IL-1β and IFN-γ predicted increased fatigue one month later(74). However, they did not include daily stressor, worrying, cortisol and pro-inflammatory cytokines in a single model. A recent multivariate analysis of a SLE cohort without concomitant fibromyalgia showed that stress, depression and pain independently correlated with fatigue(75), with stress being the largest contributor to fatigue whilst disease activity did not contribute. However, another study in SLE concluded that pain, social support and depression predict fatigue, but perceived stress did not(76).

Dysfunction of the hypothalamic-pituitary-gonadal (HPG), and hypothalamic-pituitary-thyroid (HPT) axes have also been reported in pSS, SLE and RA (77, 78) although their relationships with fatigue was not examined (79).

Autonomic Nervous System (ANS)

The ANS plays a vital role in adaptive responses to stressors through its ability to implement anticipatory actions rapidly. Inflammation activates pattern-recognition receptors which in turn stimulate the vagus nerve, resulting in the release of norepinephrine. Norepinephrine activates a special T cell subset which produces acetylcholine and inhibit pro-inflammatory cytokine production by macrophages (Figure 2C)(80). In general, the sympathetic nervous system (SNS) triggers the "fight or flight" response to enable rapid reactions to a threat, whereas the parasympathetic nervous system (PNS) tends to limit stress reactions and restore equilibrium once the threat has passed. Catecholamines play an important role in regulation of energy mobilization and utility and cardiovascular function (which control supply of fuel to tissues). Imbalances between the SNS and PNS may lead to hyper-arousal, emotional changes and attenuated heart rate variability(81). Both symptoms of dysautonomia as well as objective measures of autonomic dysfunction were common in pSS and were associated with fatigue(82-91). Of note, over 40% of pSS patients had decreased parasympathetic activities(84). More interestingly, non-invasive vagus nerve stimulation (VNS) twice daily for 4 weeks was accompanied by improvement in fatigue in pSS patients(92). These observations support a role for the ANS, particularly the vagus nerve, in the modulation of fatigue.

Autonomic dysfunction has also been reported in other IRD, however, the relationship with fatigue was not explored(93-95). In RA, VNS is associated with a clinical improvement and reduction in inflammatory cytokines although effect on fatigue was not measured(96, 97).

Sleep

Sleep disturbances affect 40-75% of patients with rheumatic diseases and are often associated with fatigue(98).

Sleep disturbances in patients with RA are characterised by worse sleep efficiency (SE), sleep quality, sleep latency, number of awakenings, and time awake after sleep compared to healthy control groups(99, 100). The relationship between fatigue and sleep is not fully defined but a bi-directional relationship is likely, with poor sleep leading to fatigue and daytime fatigue resulting in sleep disturbances (101, 102).

Sleep also has a complex relationship with inflammation, HPA axis, ANS and mood disorders(101). As mentioned, inflammation affects neuroendocrine synthesis such as monoamines, melatonin, prolactin, and growth hormone, all of which can affect sleep(103). In SLE, sleep disorders appear to be associated with disease activity alongside pain and fatigue(104). In pSS, poor sleep is prevalent and associated with high levels of symptom burden, orthostatic symptoms and fatigue(105).

Sleep disturbance is associated with altered HPA activity and cortisol level, and changes in the circadian pattern of circulating levels of cortisol in turn regulate sleep(106). Sleep disruption is associated with activation of the SNS. The relationship between sleep, HPA axis and ANS however is complex and influenced by factors such as chronicity and type of sleep disruption(101).

Metabolic disturbances

Oxidative stress refers to an imbalance of pro-oxidants and antioxidants in favour of the former(107) whereas nitrosative stress is characterized by overproduction of nitric oxide (·NO)(108). Inflammation increases oxidative and nitrosative stress through inducing the production of free radicals and reactive intermediates of oxygen and nitrogen. Measurement of F2-isoprostane has been used to assess the levels of oxidative stress. Both urine and plasma F2-isoprostane were associated with fatigue in lupus patients(109). Shah et al. showed that the activities of antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and the antioxidant molecule glutathione (GSH) were significantly reduced in SLE patients compared to controls(110). The precise mechanisms by which increased oxidative or nitrosative stress results in fatigue, however, were unclear. Possible mechanisms include attenuating aerobic metabolic capacity and reducing muscle force production(111). Antioxidant supplementation has been shown to improve exercise performance and reduce muscle fatigue(112, 113).

Cardiopulmonary fitness, physical activity, Body Mass Index (BMI)

Reduced physical activity is a hallmark of fatigue. Since cardiopulmonary fitness and BMI are key predictors of physical activity, their roles in fatigue have also been examined. Dassouki et al reported that female pSS

patients (n=29) had lower VO_2peak, muscle strength and function and higher levels of fatigue compared to aged-matched healthy women (n=20)(114). Physical activity levels (measured using accelerometer) were comparable, and there was no significant correlation between fatigue and VO_2peak or muscle strength/function or physical activity (step counts or duration of different levels of physical activity). However, fatigue was measured using FACIT-F, which may not be the most appropriate tool for analysing the relationship between fatigue and these objective measurements. Furthermore, the author only performed bivariate correlation analysis without taking into consideration of potential confounders(114). In a randomised controlled trial of supervised walking in pSS patients, improvement in VO_2max and cardiovascular fitness is associated with reduction of fatigue and depression(115). Reduction of cardiopulmonary fitness could be a consequence of reduced physical activity due to fatigue and musculoskeletal pain. Data from the 273 patients of the UK primary Sjogren's syndrome registry(116) revealed that self-reported physical activity levels at all intensity levels were reduced among pSS patients compared to age and gender matched healthy controls. Furthermore, reduced moderate and vigorous physical activity levels were associated with fatigue(117). Consistently, Wouter et al found that reduced physical activity, activity avoidance and somatic focus were associated with fatigue among pSS patients(118). These findings were confirmed using data from accelerometers to measure habitual physical activity levels.

Poor exercise tolerance and reduced maximum aerobic capacity were also observed in SLE and RA patients(119, 120) . In a study of 443 RA patients, Loppenthin and co-workers showed that 78% were mainly sedentary or having a low level of physical activity, which is significantly higher than the general Danish population. Physical fatigue is the strongest predictor of reduced physical activity(121). Increased physical activity is associated with improved cardiorespiratory fitness and reduced fatigue in RA(122). A meta-analysis and subsequent review conducted by Cramp et al concluded that physical activity potentially improve fatigue in RA, albeit the effect size was described as small-to-moderate (123, 124). Furthermore, whilst physical activity intervention appeared to improve fatigue in RA patients; these trials were often performed over a short period of time (typically < 12 weeks) without evidence of sustained improvement. Longer interventions have been implemented in patients with SLE with two studies using a home exercise intervention over a period of 8 and 12 weeks, both led to reductions in fatigue(125, 126) which was sustained at 3 months if participants continued to exercise(126).

Obesity is a predictor of fatigue in RA(127-129) and SLE(130, 131). The association between obesity and fatigue is interesting from the perspective of energy management. Obesity represents a balance against energy expenditure in favour of energy conservation. Accumulation of adipose tissues in obesity represents a surplus of energy. Paradoxically, obese individuals experience fatigue and decreased physical endurance, reflecting an "energy deficiency state". Interestingly, EMG studies showed a greater reduction of voluntary activation of available motor units in obese participants when fatigued suggesting a stronger component of CNS-mediated fatigue(132). Other possible mechanisms include altered energy distribution or production and mitochondrial dysfunction, particularly in skeletal muscles. Obesity could also contribute to both oxidative stress and fatigue by increasing the inflammatory burden(133). However, obesity is associated with several determinants of health including the social and economic environment, the physical environment, and the person's individual characteristics and behaviours. The relationship between obesity and fatigue is an example of potentially interacting factors at intra-individual, inter-individual and societal levels.

Peripheral muscles

Fatigued patients often describe that their muscles feel week and unable to sustain prolonged or vigorous activities. Reduced muscle strength and endurance are well documented in patients with inflammatory arthritis and correlate with disease activity and reduced physical activity (134). Sarcopenia and myositis (including subclinical myositis, and elevated serum creatine kinase) can occur in many IRD(135-138), which may also contribute to fatigue.

More subtle changes in peripheral muscle have also been implicated in fatigue in other chronic diseases. For instance, using ^{31}P magnetic resonance spectroscopy to define mitochondrial function and pH regulation in peripheral muscle during exercise at sub-maximal voluntary contraction, Hollingsworth *et al* showed that patients with primary biliary cirrhosis exhibited excess acidosis after exercise indicating muscle mitochondrial dysfunction. Furthermore, the extent to which patients can recover rapidly from acidosis was associated with fatigue(139, 140). The same group also showed that patients with chronic fatigue syndrome (CFS) had substantial impairment in recovery from intramuscular acidosis following exercise(137-139).

Psychosocial determinants

Mood disturbances

Depression is more prevalent in rheumatic diseases compared to the general population(141). Many factors can contribute to the occurrence of comorbid depression, such as shared genetic factors, converging biological pathways, social factors, health behaviours and psychological factors(142). Depression is also strongly linked with fatigue in IRD(26, 28, 35, 75, 76, 143, 144) as well as non-inflammatory diseases(145).

It is worth noting that fatigue is one of the diagnostic criteria for depression(146). However, while it is possible that fatigue can contribute to depression via shared mechanistic pathways and consequences on daily life, depression and fatigue are distinct phenomena(147) and many fatigued patients do not suffer from significant depression(29). Despite this, it can still be a challenge to distinguish depression from fatigue clinically. Depression is primarily mental, and the main signs include sad mood, social isolation and negative thoughts, sometimes accompanied by physical symptoms such as headaches, cramps and stomach upsets. Fatigue is often a feature, but not the primary symptom. It is common for patients with depression to experience anhedonia (the loss of interest in activities that people used to enjoy and a decreased ability to feel pleasure). Consequently, they can be uninterested in taking part in activities, irrespective of the task or the amount of effort it requires. By contrast, fatigue is primarily physical and many patients report wanting to engage in activities but feeling too tired to do so.

Inflammation has been implicated in the pathogenesis of depression based on findings such as increased circulating pro-inflammatory cytokines and microglial activation in the brain from post-mortem and in vivo imaging studies(148). To what extent inflammation mediate all depressive illness remains unclear. It is noteworthy that adverse childhood events can result in immune activation(149) raising the possibility of a bi-directional relationship between depressive illness and inflammation. Furthermore, whether the same mechanisms by which inflammation mediating depressive symptoms are shared with those mediating fatigue is unclear. In this regard, the IL-1β pathway is a candidate mechanism linking depression and fatigue at a molecular level(150, 151).

Pain

Pain occurs as a complex interplay between peripheral and central connections, biological influences such as pro-inflammatory cytokines alongside the psychological perception of pain(151, 152). Musculoskeletal pain is often a defining feature is many IRD(36, 153, 154)and is a key predictor of fatigue in many studies(26, 28, 35, 75, 76). Data from clinical trials further underlined the relationship between pain and fatigue. In RA, improvement in fatigue may be driven by pain reduction from disease-modifying agents(35). However, the causal link between pain and fatigue is not proven, and it has been suggested that fatigue can also enhance pain(151). Similar to fatigue, pain constitutes a survival mechanism and is an alarm system of ongoing or impending damage. Therefore, pain and fatigue may be two symptoms of a coordinated response of the body to chronic stressors with shared underlying mechanisms. It has also been suggested that pain is an activator rather than a consequence of the sickness response, leading to a state of hyperalgesia to enable the body remains vigilant against an outside threat. The model stipulates that peripheral pain leads to the production of cytokines, specifically IL-1β, which then drives a fatigue response(151).

Life events, perception and other psychosocial factors

Adverse life events whether in early or adult life, access to psychosocial support, relationship status, income and educational levels are associated with fatigue in chronic diseases(155). Additionally, coping strategies and attitudes to illness have been linked with fatigue. One example is learned helplessness (an attributional style whereby a person perceives that they have little control over the events in their life and so responds passively to the challenges that they face) which has been shown to predict fatigue in recent-onset inflammatory polyarthritis(156). Tendency to catastrophizing, avoidance and negative illness perception or belief is associated with of fatigue in many chronic diseases(157, 158). The mechanism(s) linking these factors to the development or maintenance of fatigue is unclear. However, it is helpful to understand which psychosocial factors are amenable to intervention and can contribute to effective fatigue self-management(159). Indeed, the most promising results of fatigue management in RA to date came from cognitive-behavioural therapy (CBT), which showed both short- and long- term benefit(159, 160). Premorbid level of fatigue is a key predictor of cancer-related fatigue. Data on premorbid levels of fatigue in IRD are rarely available. This observation, however, supports the notion that the susceptibility to fatigue may be influenced by genetics, previous

exposure to stressors including adverse life events, psychosocial factors and fatigue-associated comorbid conditions.

The study of psychosocial factors in fatigue can be challenging and considered “less exciting or scientific” by some researchers or even “trivialising” the seriousness of fatigue by some patients. There can also be stigma around psychological factors which can contribute to the privileging of physical over mental aspects of health. At a research level, this can influence agendas and resources. At the care provision level, this preference can be enacted by both patients and clinicians (e.g., in a consultation) and at a system level (e.g., in commissioning services). However, psychological and social factors are not merely epiphenomena and our emotions and feelings are no less “real” than genes and molecules. The concept of “self” consists not only a “neuro-biological self” but also a “psychological self” that intricately linked to each other. For instance, a recent meta-analysis suggests that “mindfulness” is associated with reduction of pro-inflammatory biomarkers in blood and in saliva(161). There is a growing shift in emphasis on the neurobiological changes associated with thoughts, emotions or feelings as potential therapeutic targets. However, such an approach is not without potential pitfalls if the thoughts and emotions are the triggers of those neurobiological changes. As an illustration, the conscious decision to move our right hand will activate the left motor cortex which sends signals to the right hand muscles. Electromagnetic stimulation of the left motor cortex will also cause our right hand to move, but it is unlikely to cause us to “make a conscious decision”. Therefore, the critical issues are whether thoughts, emotions and feelings are the cause or consequence of the associated neurobiological changes and whether they are amenable therapeutically. The evidence for cognitive-behavioural approaches in reducing fatigue suggests that cognitions can be helpfully re-framed using Socratic questioning to promote a change in beliefs and enhanced coping(159). This leads to better knowledge, confidence, and reactivation in everyday activities. The use of daily activity diaries for patients to monitor their energy expenditure and individualised goal setting lends weight to the argument that a “personalised" and "holistic" approach is likely to be needed to optimally manage fatigue. As fatigue research progresses, we believe that psychosocial factors deserve more attention but require a multi-disciplinary and open-minded approach.

Mechanistic and conceptual model of fatigue

In building a mechanistic and a conceptual model of fatigue for IRD, we sought to explain several key observations (Box 3).

Mechanistic model of fatigue

Our being (which includes the "physical" and "psychological" self) consists of many interconnecting functional systems. Any stressor to our being will elicit a coordinated response from several functional systems, even if the stressor was directed primarily to one system. For instance, a simple cut to the skin will trigger responses from multiple systems – vasoconstriction and coagulation system activation to stop blood loss, inflammatory cascade to prevent infection, nociceptive system and SNS activation to alert and prepare our body of danger. Thus, it is unsurprising that in chronic IRD, multiple functional systems are affected. However, to determine how these different functional systems contribute to fatigue is challenging.

Figure 3 is a diagrammatic summary of a possible mechanistic model of fatigue in IRD. Since inflammation is the central pathology in these conditions, it is likely that inflammation is the key driver of fatigue through several inter-connecting biopsycho-physiological mechanisms. The relationship between inflammation and these various mechanisms are likely bi-directional. As the underlying inflammatory condition becomes chronic, additional adaptive mechanisms may be involved as the body attempts to reach a new equilibrium. In fatigued individuals, such (mal)adaptive responses may perpetuate fatigue, and possibly suppressing inflammation at the same time, providing a potential explanation for the observation of the inverse relationship between circulating pro-inflammatory cytokines and fatigue severity. At this chronic stage, systemic inflammation may play a much lesser or even no role in the maintenance of fatigue. However, an acute disease flare may disturb the established equilibrium, and systemic inflammation may again contribute to fatigue.

Since some patients experience minimal or no fatigue despite ongoing systemic inflammation (29), inflammation alone is insufficient to cause fatigue. Furthermore, fatigue is prevalent in many chronic conditions in which evidence for an inflammatory basis is weak, and yet very similar "predictors" of fatigue were identified(162, 163). Moreover, a recent study of fatigue across five chronic conditions (RA, heart failure, multiple sclerosis, chronic kidney disease and chronic obstructive pulmonary disease) found that the

qualitative experience of fatigue is similar across these conditions(15). In addition, the "unpredictability" and "variability" of fatigue from "moments to moments" experienced by many patients is also difficult to be explained by a mechanistic model centred solely on inflammation. We hypothesised that inflammation is one of the many interconnecting mechanisms that contribute to the development of fatigue in response to external or internal stressors to the body (Figure 1). Consistently, circulating levels of the stress protein HSP-90α was significantly elevated in fatigued pSS patients compared to their non-fatigued counterparts. Furthermore, together with depression, the plasma levels of HSP-90α were independent predictors of fatigue in a multi-regression model(148).

The ANS, the HPA axis and the immune system are key to the body's response to bio-physiological and psychosocial stressors and are likely to be the key systems involved in the initiation of a complex network of responses that contribute to fatigue. For instance, adept at providing rapid reactions to a threat and engage the body in anticipatory actions, the ANS may play a key role in the day-to-day (even hour-to-hour) variability of fatigue severity. In contrast, the HPA-axis and immune systems, being less flexible than the ANS(164), may contribute to other facets of fatigue.

Different types or subsets of fatigue have been proposed. However, patients presenting with a single "type/subset" of fatigue without manifestation of other "types/subsets" of fatigue is rare. Our view is that different "types/subsets" of fatigue are different dimensions of the same symptom and the relative manifestations of each dimension/subsets/types of fatigue may depend on the relative contribution of different mechanisms mentioned in Figure 3. We also need to consider individual differences in how patients interpret and respond to fatigue, which further complicates identification of the underlying mechanisms.

Conceptual model of fatigue

What is the physiological or functional significance of fatigue in chronic conditions? Fundamentally, fatigue is a description of an inability to achieve the expected or maximal levels of performance. Fatigue is often considered as part of the sickness behaviour complex in response to inflammation, and chronic fatigue being a consequence of maladaptive sickness behaviour. However, fatigue is not a "condition" in which a person either has or not, but a continuum. Therefore, we believe that fatigue is a bio-psycho-physiological state reflecting

the body's overall strategy in resource (energy) management. These resources include energy needed for physical activities and other bodily function, cognition as well as emotions, providing an explanation for the multi-dimensional nature of fatigue. Fatigue occurs when the body adopts a strategy that limit resource utilisation ("rationing") in order to "conserve energy" for sustained threat. Interestingly, in the qualitative metasynthesis of experience of fatigue mentioned earlier, the most prominent themes are "running out of batteries" and "Bad Life (restrictions in their ability to engage in physical and social activities)"(15). This is consistent with our model that in fatigued patients, they perceived a (relative) lack of energy/resources within their body and therefore in the context of perceived sustained threat, their body adopt a rationing approach to restrict energy use for essential activities at the expense of other activities such as leisure.

Furthermore, resource management is part of a coordinated bio-psycho-physiological response to the perceived current and anticipated stress. Therefore, fatigue may be accompanied by adaptive responses of other systems – e.g. altered ANS activity to prepare the body in "fight or flight" mode, altered pain sensitivity to detect danger, changes to the immune system to defend the body, changes to diurnal rhythm to maintain "arousal" etc.

We further propose that several factors may determine our body's resource management strategy. These include the perceived current stressor/danger, the anticipatory stressor/danger, the assessment of the bio-physiological state of the body (interoception), any previous exposure to stressor/danger and their outcomes, and various other factors (such as genetics, environmental, etc.) In addition, perceptions and related behavioural responses are shaped by individual beliefs and expectations and cultural norms.

How does this model explain fatigue persistence despite the underlying disease is in remission? There are several non-mutually exclusive possibilities. Firstly, clinical remission may not equate to molecular remission. Furthermore, in the context of IRD, the break in immune tolerance may not have been restored, thus the "threat" remains. After all, resource management has much to do with planning for future (perceived threat) as for the present. Additionally, there may be irreversible / semi-permanent changes in some of the mechanistic pathways that mediate fatigue (e.g. through epigenetic changes, changes in neural connections, depletion of certain proteins or other bioactive substances). Furthermore, other comorbidities may have developed. For instance, chronic fatigue may lead to reduced cardiovascular fitness or sleep disorders. Finally, factors such as genetics, past medical/life history, other psychosocial factors may increase the susceptibility of

an individual to fatigue. If fatigue reflects the resource management of the body, our genetic make-up and past medical and life events might shape our interoception and anticipatory danger perception.

Psychologically, we see that over time, patients' coping resources can reduce and this can impact their experiences of fatigue. As well as fatigue and flares, other health and life circumstances can undermine coping. We can see patients whose IRD has been stable, but their coping is not stable, and the distress that they have been experiencing has been slowly increasing. It might not be a steady and gradual deterioration, but rather a person's coping with their IRD may not fully recover from a setback even though their symptoms return to the plateau they had before. Each setback represents a step down from which the person does not rise afterwards when the root cause has passed. They might withdraw from some social activity, give up some form of regular exercise or increase their reliance on medication, all of which can exacerbate or maintain fatigue.

Summary and future directions

Fatigue is a prevalent, disabling, and difficult to manage symptom for patients with IRD as well as many other rheumatic and non-rheumatic conditions. Whilst we have focussed our discussion of the contributing mechanisms on IRD, similar findings are reported in other fatigue-related conditions with a diverse underlying pathogenetic mechanisms such as cancer, multiple sclerosis, chronic renal failure and fibromyalgia(4, 165, 166). Our proposed mechanistic and conceptual models of fatigue may also be relevant to fatigue in other chronic conditions which we hope will provide a useful framework for future research. Future studies investigating these common strands of fatigue pathogenesis may help to identify targets for interventions across multiple chronic diseases.

There is an urgent need to develop consensus and recommendations on how to define and measure fatigue to provide a broad framework covering different dimensions of fatigue. We propose the following definition of fatigue as a starting point for discussion: "***A multi-dimensional phenomenon in which the biophysiological, cognitive, motivational and emotional state of the body is affected resulting in significant impairment of the individual's ability to function in their normal capacity***". Recommendations on the data types to be included and reported in fatigue research will facilitate harmonisation of datasets for comparison and meta-analysis.

Caution is needed in extrapolating findings based on experimental models of “induced” “physiological” fatigue unless they have been replicated in patients with “pathological” fatigue. This is because many “induced fatigue” models are transient and self-limiting, unlike fatigue in chronic conditions which is often long-standing and not relieved by rest. Given the levels of our understanding of this complex phenomenon remains relatively poor, such framework should be reviewed periodically as our knowledge on fatigue advances. Research to identify objective fatigue biomarkers may complement conventional questionnaire-based fatigue assessment and help to gain further insight into the pathophysiology of fatigue. Finally, given the complexity of the underlying mechanisms of fatigue, future research should ideally involve multi-disciplinary expertise that enable different mechanisms and confounding factors be investigated concurrently, and with adequate sample size. Such studies likely require substantial financial and human resources and commitment.

Figure legends

Figure 1. Putative mechanisms implicated in the pathogenesis of fatigue.

Figure 2. The role of (A) CNS; (B) HPA axis; and (C) ANS in fatigue.

A. CNS

Circulating pro-inflammatory cytokines may lead to microglia activation in the brain. This could be achieved through direct transfer of cytokines across the blood brain barrier via various mechanisms (receptor-mediated transcytosis, leakage across damaged tight junction or circumventricular organ), or indirectly via other pathways, such as activated vascular endothelial cells or the vagus nerve. Pro-inflammatory activities in the brain in turn results in several changes which include:

- inhibition of the release of the neurotransmitter noradrenaline, which is important for increasing arousal, alertness and attention.
- increased uptake and breakdown of the monoamines (serotonin, dopamine and noradrenaline) and reducing their availability in the synaptic cleft
- increased tryptophan-2,3-dioxygenase and indoleamine-2,3-dioxygenase (IDO) which promote tryptophan (TRP) into the kynurenine (KYN) metabolic pathway. These metabolites of the KYN pathway further induce local inflammation in the brain.

B. HPA Axis:

Stress and pro-inflammatory can both stimulate the hypothalamus leading to the release of corticotrophin-releasing hormone (CRH), which acts on the anterior pituitary gland to release adrenocorticotrophin releasing hormone (ACTH). ACTH enters the circulation and stimulates the adrenal gland to release cortisol. Cortisol has several effects on the body. Cortisol inhibits inflammation, promotes the release of amino acids, free fatty acids (FFA) and glucose into the circulation which in turn enhances oxidative stress. , . Cortisol alsoaffectsthe mood.

C. ANS

Stress leads to the stimulation of inflammation and of the sympathetic nervous system. Specifically, it antagonises the effect of the parasympathetic nervous system and primes the cardiovascular system to optimize cardiac output. SNS activation leads to shifts in metabolism and the release of glucose and lactate, leading to oxidative stress. The emotional alertness from the SNS leads to the 'fight-or-flight' behaviour, resulting in hyperarousal, anxiety, and sleep disturbance.

Inflammation activates pattern-recognition receptors which in turn stimulate the vagus nerve, resulting in the release of norepinephrine. Norepinephrine activates a special T cell subset which produces acetylcholine and inhibit pro-inflammatory cytokine production by macrophages. The parasympathetic nervous system (PNS) tends to limit stress reactions and restore equilibrium once the threat has passed. Imbalances between the SNS and PNS may lead to hyper-arousal, emotional changes and attenuated heart rate variability.

Figure 3. Mechanistic model of fatigue.

See main text for details.

Glossary terms

- ***Sickness behaviour*** - refers to the adaptive behaviours developed by animals (and humans) during an acute infection that are presumed to be beneficial for recovery and survival. Such behaviours typically include social withdrawal, reduced general activities and spending more time sleeping. It is accompanied by symptoms of fatigue, depression, hyperalgesia, reduced appetite and sleepiness.

- ***Dysautonomia*** – an umbrella term used to describe conditions due to malfunctioning of the Autonomic Nervous System (ANS). Symptoms associated with dysautonomia vary, depending on the component(s) of the ANS being affected.

References

1. Overman CL, Kool MB, Da Silva JAP, Geenen R. The prevalence of severe fatigue in rheumatic diseases: an international study. Clinical rheumatology. 2016;35(2):409-15.
2. Dures E, Fraser I, Almeida C, Peterson A, Caesley J, Pollock J, et al. Patients' Perspectives on the Psychological Impact of Inflammatory Arthritis and Meeting the Associated Support Needs: Open-Ended Responses in a Multi-Centre Survey. Musculoskeletal care. 2017;15(3):175-85.
3. Dures E, Almeida C, Caesley J, Peterson A, Ambler N, Morris M, et al. Patient preferences for psychological support in inflammatory arthritis: a multicentre survey. Annals of the rheumatic diseases. 2016;75(1):142-7.
4. Swain MG. Fatigue in chronic disease. Clin Sci (Lond). 2000;99(1):1-8.
5. Druce KL, Basu N. Predictors of fatigue in rheumatoid arthritis. Rheumatology. 2019;58(Supplement_5):v29-v34.
6. Meijer JM, Meiners PM, Huddleston Slater JJ, Spijkervet FK, Kallenberg CG, Vissink A, et al. Health-related quality of life, employment and disability in patients with Sjogren's syndrome. Rheumatology (Oxford, England). 2009;48(9):1077-82.
7. Westhoff G, Dörner T, Zink A. Fatigue and depression predict physician visits and work disability in women with primary Sjögren's syndrome: results from a cohort study. Rheumatology. 2012;51(2):262-9.
8. McCormick N, Marra CA, Sadatsafavi M, Kopec JA, Aviña-Zubieta JA. Excess Productivity Costs of Systemic Lupus Erythematosus, Systemic Sclerosis, and Sjögren's Syndrome: A General Population-Based Study. Arthritis care & research. 2019;71(1):142-54.
9. Basu N, McClean A, Harper L, Amft EN, Dhaun N, Luqmani RA, et al. Markers for work disability in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatology (Oxford, England). 2014;53(5):953-6.
10. Borrell-Carrió F, Suchman AL, Epstein RM. The biopsychosocial model 25 years later: principles, practice, and scientific inquiry. Annals of family medicine. 2004;2(6):576-82.
11. Hackett KL, Newton JL, Frith J, Elliott C, Lendrem D, Foggo H, et al. Impaired functional status in primary Sjogren's syndrome. Arthritis care & research. 2012;64(11):1760-4.
12. Hewlett S, Cockshott Z, Byron M, Kitchen K, Tipler S, Pope D, et al. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis and rheumatism. 2005;53(5):697-702.
13. Primdahl J, Hegelund A, Lorenzen AG, Loeppenthin K, Dures E, Appel Esbensen B. The Experience of people with rheumatoid arthritis living with fatigue: a qualitative metasynthesis. BMJ Open. 2019;9(3):e024338.
14. Jones DEJ, Gray JC, Newton J. Perceived fatigue is comparable between different disease groups. QJM: An International Journal of Medicine. 2009;102(9):617-24.
15. Jaime-Lara RB, Koons BC, Matura LA, Hodgson NA, Riegel B. A Qualitative Metasynthesis of the Experience of Fatigue Across Five Chronic Conditions. Journal of pain and symptom management. 2020;59(6):1320-43.
16. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). Arthritis care & research. 2011;63 Suppl 11:S263-86.
17. Santos EJF, Duarte C, da Silva JAP, Ferreira RJO. The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. Rheumatology (Oxford, England). 2019;58(Suppl 5):v3-v9.
18. Geenen R, Dures E. A biopsychosocial network model of fatigue in rheumatoid arthritis: a systematic review. Rheumatology. 2019;58(Supplement_5):v10-v21.
19. Ng W-F, Bowman SJ. Primary Sjögren's syndrome: too dry and too tired. Rheumatology. 2010;49(5):844-53.
20. Ahn GE, Ramsey-Goldman R. Fatigue in systemic lupus erythematosus. Int J Clin Rheumtol. 2012;7(2):217-27.
21. Pope JE. Management of Fatigue in Rheumatoid Arthritis. RMD Open. 2020;6(1).
22. Korte SM, Straub RH. Fatigue in inflammatory rheumatic disorders: pathophysiological mechanisms. Rheumatology. 2019;58(Supplement_5):v35-v50.
23. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature reviews Neuroscience. 2008;9(1):46-56.

24. Lopes PC, Block P, König B. Infection-induced behavioural changes reduce connectivity and the potential for disease spread in wild mice contact networks. Scientific Reports. 2016;6(1):31790.
25. Muskardin TLW, Niewold TB. Type I interferon in rheumatic diseases. Nature reviews Rheumatology. 2018;14(4):214-28.
26. Howard Tripp N, Tarn J, Natasari A, Gillespie C, Mitchell S, Hackett KL, et al. Fatigue in primary Sjögren's syndrome is associated with lower levels of proinflammatory cytokines. RMD Open. 2016;2(2).
27. Umare V, Pradhan V, Nadkar M, Rajadhyaksha A, Patwardhan M, Ghosh KK, et al. Effect of proinflammatory cytokines (IL-6, TNF-α, and IL-1β) on clinical manifestations in Indian SLE patients. Mediators of inflammation. 2014;2014:385297.
28. Davies K, Mirza K, Tarn J, Howard-Tripp N, Bowman SJ, Lendrem D, et al. Fatigue in primary Sjogren's syndrome (pSS) is associated with lower levels of proinflammatory cytokines: a validation study. Rheumatol Int. 2019;39(11):1867-73.
29. Tarn JR, Howard-Tripp N, Lendrem DW, Mariette X, Saraux A, Devauchelle-Pensec V, et al. Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. The Lancet Rheumatology. 2019;1(2):e85-e94.
30. Posada J, Valadkhan S, Burge D, Davies K, Tarn J, Casement J, et al. Improvement of Severe Fatigue Following Nuclease Therapy in Patients With Primary Sjögren's Syndrome: A Randomized Clinical Trial. Arthritis & rheumatology (Hoboken, NJ). 2021;73(1):143-50.
31. James K, Al-Ali S, Tarn J, Cockell SJ, Gillespie CS, Hindmarsh V, et al. A Transcriptional Signature of Fatigue Derived from Patients with Primary Sjögren's Syndrome. PLoS ONE. 2015;10(12):e0143970.
32. Da Costa D, Dritsa M, Bernatsky S, Pineau C, Ménard HA, Dasgupta K, et al. Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioral and psychosocial factors. The Journal of rheumatology. 2006;33(7):1282-8.
33. Bruce IN, Mak VC, Hallett DC, Gladman DD, Urowitz MB. Factors associated with fatigue in patients with systemic lupus erythematosus. Annals of the rheumatic diseases. 1999;58(6):379-81.
34. Tench C, McCurdie I, White P, d'Cruz D. The prevalence and associations of fatigue in systemic lupus erythematosus. Rheumatology. 2000;39(11):1249-54.
35. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology (Oxford, England). 2006;45(7):885-9.
36. Lendrem D, Mitchell S, McMeekin P, Gompels L, Hackett K, Bowman S, et al. Do the EULAR Sjögren's syndrome outcome measures correlate with health status in primary Sjögren's syndrome? Rheumatology (Oxford, England). 2015;54(4):655-9.
37. Druce KL, Bhattacharya Y, Jones GT, Macfarlane GJ, Basu N. Most patients who reach disease remission following anti-TNF therapy continue to report fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford, England). 2016;55(10):1786-90.
38. Almeida C, Choy EH, Hewlett S, Kirwan JR, Cramp F, Chalder T, et al. Biologic interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev. 2016(6):Cd008334.
39. Devauchelle-Pensec V, Pennec Y, Morvan J, Pers JO, Daridon C, Jousse-Joulin S, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis care & research. 2007;57(2):310-7.
40. Dass S, Bowman SJ, Vital EM, Ikeda K, Pease CT, Hamburger J, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Annals of the rheumatic diseases. 2008;67.
41. Carubbi F, Cipriani P, Marrelli A, Benedetto PD, Ruscitti P, Berardicurti O, et al. Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study. Arthritis Research & Therapy. 2013;15(5):R172.
42. St Clair EW, Levesque MC, Luning Prak ET, Vivino FB, Alappatt CJ, Spychala ME, et al. Rituximab Therapy for Primary Sjögren's Syndrome: An Open-Label Clinical Trial and Mechanistic Analysis. Arthritis and rheumatism. 2013;65(4):1097-106.
43. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, et al. Treatment of primary sjögren syndrome with rituximab: A randomized trial. Annals of Internal Medicine. 2014;160(4):233-42.
44. Bowman SJ, Everett CC, O'Dwyer JL, Emery P, Pitzalis C, Ng WF, et al. Randomized Controlled Trial of Rituximab and Cost-Effectiveness Analysis in Treating Fatigue and Oral Dryness in Primary Sjogren's Syndrome. Arthritis & rheumatology (Hoboken, NJ). 2017;69(7):1440-50.

45. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721-31.
46. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis and rheumatism. 2011;63(12):3918-30.
47. Bangert E, Wakani L, Merchant M, Strand V, Touma Z. Impact of belimumab on patient-reported outcomes in systemic lupus erythematosus: review of clinical studies. Patient Relat Outcome Meas. 2019;10:1-7.
48. Strand V, Berry P, Lin X, Asukai Y, Punwaney R, Ramachandran S. Long-Term Impact of Belimumab on Health-Related Quality of Life and Fatigue in Patients With Systemic Lupus Erythematosus: Six Years of Treatment. Arthritis care & research. 2019;71(6):829-38.
49. Russell A, Hepgul N, Nikkheslat N, Borsini A, Zajkowska Z, Moll N, et al. Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome. Psychoneuroendocrinology. 2019;100:276-85.
50. Sharpe M, Wilks D. Fatigue. BMJ. 2002;325(7362):480.
51. Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL. Neural Contributions to Muscle Fatigue: From the Brain to the Muscle and Back Again. Med Sci Sports Exerc. 2016;48(11):2294-306.
52. Quan N, Banks WA. Brain-immune communication pathways. Brain Behav Immun. 2007;21(6):727-35.
53. Stetler RA, Gan Y, Zhang W, Liou AK, Gao Y, Cao G, et al. Heat shock proteins: cellular and molecular mechanisms in the central nervous system. Progress in neurobiology. 2010;92(2):184-211.
54. Yamashita M, Yamamoto T. Tryptophan circuit in fatigue: From blood to brain and cognition. Brain Research. 2017;1675:116-26.
55. Åkesson K, Pettersson S, Ståhl S, Surowiec I, Hedenström M, Eketjäll S, et al. Kynurenine pathway is altered in patients with SLE and associated with severe fatigue. Lupus Science & Medicine. 2018;5(1).
56. Schröcksnadel K, Wirleitner B, Winkler C, Fuchs D. Monitoring tryptophan metabolism in chronic immune activation. Clinica chimica acta; international journal of clinical chemistry. 2006;364(1-2):82-90.
57. Karageorgas T, Fragioudaki S, Nezos A, Karaiskos D, Moutsopoulos HM, Mavragani CP. Fatigue in Primary Sjogren's Syndrome: Clinical, Laboratory, Psychometric, and Biologic Associations. Arthritis care & research. 2016;68(1):123-31.
58. Strasser B, Geiger D, Schauer M, Gatterer H, Burtscher M, Fuchs D. Effects of Exhaustive Aerobic Exercise on Tryptophan-Kynurenine Metabolism in Trained Athletes. PLOS ONE. 2016;11(4):e0153617.
59. Malhotra R, Persic V, Zhang W, Brown J, Tao X, Rosales L, et al. Tryptophan and Kynurenine Levels and Its Association With Sleep, Nonphysical Fatigue, and Depression in Chronic Hemodialysis Patients. Journal of Renal Nutrition. 2017;27(4):260-6.
60. Larssen E, Brede C, Hjelle A, Tjensvoll AB, Norheim KB, Bårdsen K, et al. Fatigue in primary Sjögren's syndrome: A proteomic pilot study of cerebrospinal fluid. SAGE Open Med. 2019;7:2050312119850390-.
61. Harboe E, Tjensvoll AB, Vefring HK, Gøransson LG, Kvaløy JT, Omdal R. Fatigue in primary Sjögren's syndrome – A link to sickness behaviour in animals? Brain, Behavior, and Immunity. 2009;23(8):1104-8.
62. Bårdsen K, Brede C, Kvivik I, Kvaløy JT, Jonsdottir K, Tjensvoll AB, et al. Interleukin-1-related activity and hypocretin-1 in cerebrospinal fluid contribute to fatigue in primary Sjögren's syndrome. Journal of Neuroinflammation. 2019;16(1):102.
63. Schrepf A, Kaplan CM, Ichesco E, Larkin T, Harte SE, Harris RE, et al. A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. Nature Communications. 2018;9(1):2243.
64. Basu N, Murray AD, Jones GT, Reid DM, Macfarlane GJ, Waiter GD. Neural correlates of fatigue in granulomatosis with polyangiitis: a functional magnetic resonance imaging study. Rheumatology (Oxford, England). 2014;53(11):2080-7.
65. Kraynak TE, Marsland AL, Wager TD, Gianaros PJ. Functional neuroanatomy of peripheral inflammatory physiology: A meta-analysis of human neuroimaging studies. Neurosci Biobehav Rev. 2018;94:76-92.
66. Goñi M, Basu N, Murray AD, Waiter GD. Neural Indicators of Fatigue in Chronic Diseases: A Systematic Review of MRI Studies. Diagnostics (Basel, Switzerland). 2018;8(3).
67. Kutlubaev MA, Duncan FH, Mead GE. Biological correlates of post-stroke fatigue: a systematic review. Acta neurologica Scandinavica. 2012;125(4):219-27.
68. Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. The Journal of clinical endocrinology and metabolism. 1993;77(6):1690-4.

69. Tsigos C, Papanicolaou DA, Defensor R, Mitsiadis CS, Kyrou I, Chrousos GP. Dose effects of recombinant human interleukin-6 on pituitary hormone secretion and energy expenditure. Neuroendocrinology. 1997;66(1):54-62.
70. Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, Tzioufas AG, Moutsopoulos HM. Hypofunction of the stress axis in Sjogren's syndrome. The Journal of rheumatology. 1998;25(8):1508-14.
71. Crofford LJ, Kalogeras KT, Mastorakos G, Magiakou MA, Wells J, Kanik KS, et al. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. The Journal of clinical endocrinology and metabolism. 1997;82(4):1279-83.
72. Straub RH, Paimela L, Peltomaa R, Schölmerich J, Leirisalo-Repo M. Inadequately low serum levels of steroid hormones in relation to interleukin-6 and tumor necrosis factor in untreated patients with early rheumatoid arthritis and reactive arthritis. Arthritis and rheumatism. 2002;46(3):654-62.
73. Gutiérrez MA, Garcia ME, Rodriguez JA, Rivero S, Jacobelli S. Hypothalamic-pituitary-adrenal axis function and prolactin secretion in systemic lupus erythematosus. Lupus. 1998;7(6):404-8.
74. Evers AW, Verhoeven EW, van Middendorp H, Sweep FC, Kraaimaat FW, Donders AR, et al. Does stress affect the joints? Daily stressors, stress vulnerability, immune and HPA axis activity, and short-term disease and symptom fluctuations in rheumatoid arthritis. Annals of the rheumatic diseases. 2014;73(9):1683-8.
75. Azizoddin DR, Gandhi N, Weinberg S, Sengupta M, Nicassio PM, Jolly M. Fatigue in systemic lupus: the role of disease activity and its correlates. Lupus. 2019;28(2):163-73.
76. Jump RL, Robinson ME, Armstrong AE, Barnes EV, Kilbourn KM, Richards HB. Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. The Journal of rheumatology. 2005;32(9):1699-705.
77. Cutolo M, Sulli A, Pizzorni C, Craviotto C, Straub RH. Hypothalamic-pituitary-adrenocortical and gonadal functions in rheumatoid arthritis. Annals of the New York Academy of Sciences. 2003;992:107-17.
78. Moulton VR. Sex Hormones in Acquired Immunity and Autoimmune Disease. Front Immunol. 2018;9:2279.
79. Johnson EO, Moutsopoulos HM. Neuroendocrine manifestations in Sjögren's syndrome. Relation to the neurobiology of stress. Annals of the New York Academy of Sciences. 2000;917:797-808.
80. Sundman E, Olofsson PS. Neural control of the immune system. Advances in physiology education. 2014;38(2):135-9.
81. Porges SW. The polyvagal theory: phylogenetic substrates of a social nervous system. International journal of psychophysiology : official journal of the International Organization of Psychophysiology. 2001;42(2):123-46.
82. Brunetta E, Shiffer D, Mandelli P, Achenza S, Folci M, Zumbo A, et al. Autonomic Abnormalities in Patients With Primary Sjogren's Syndrome - Preliminary Results. Frontiers in physiology. 2019;10:1104.
83. Newton JL, Frith J, Powell D, Hackett K, Wilton K, Bowman S, et al. Autonomic symptoms are common and are associated with overall symptom burden and disease activity in primary Sjogren's syndrome. Annals of the rheumatic diseases. 2012;71(12):1973-9.
84. Koh JH, Kwok SK, Lee J, Son CN, Kim JM, Kim HO, et al. Pain, xerostomia, and younger age are major determinants of fatigue in Korean patients with primary Sjögren's syndrome: a cohort study. Scandinavian journal of rheumatology. 2017;46(1):49-55.
85. Mandl T, Wollmer P, Manthorpe R, Jacobsson LT. Autonomic and orthostatic dysfunction in primary Sjögren's syndrome. The Journal of rheumatology. 2007;34(9):1869-74.
86. Fox RI, Kang HI, Ando D, Abrams J, Pisa E. Cytokine mRNA expression in salivary gland biopsies of Sjögren's syndrome. The Journal of Immunology. 1994;152(11):5532-9.
87. Barendregt PJ, van Den Meiracker AH, Markusse HM, Tulen JH, Boomsma F, van Der Heijde GL, et al. Parasympathetic failure does not contribute to ocular dryness in primary Sjögren's syndrome. Annals of the rheumatic diseases. 1999;58(12):746-50.
88. Kovács L, Paprika D, Tákacs R, Kardos A, Várkonyi TT, Lengyel C, et al. Cardiovascular autonomic dysfunction in primary Sjögren's syndrome. Rheumatology (Oxford, England). 2004;43(1):95-9.
89. Barendregt PJ, Tulen JH, van den Meiracker AH, Markusse HM. Spectral analysis of heart rate and blood pressure variability in primary Sjögren's syndrome. Annals of the rheumatic diseases. 2002;61(3):232-6.
90. Niemelä RK, Hakala M, Huikuri HV, Airaksinen KE. Comprehensive study of autonomic function in a population with primary Sjögren's syndrome. No evidence of autonomic involvement. The Journal of rheumatology. 2003;30(1):74-9.

91. Tumiati B, Perazzoli F, Negro A, Pantaleoni M, Regolisti G. Heart rate variability in patients with Sjögren's syndrome. Clinical rheumatology. 2000;19(6):477-80.
92. Tarn J, Legg S, Mitchell S, Simon B, Ng WF. The Effects of Noninvasive Vagus Nerve Stimulation on Fatigue and Immune Responses in Patients With Primary Sjogren's Syndrome. Neuromodulation. 2019;22(5):580-5.
93. Ingegnoli F, Buoli M, Antonucci F, Coletto LA, Esposito CM, Caporali R. The Link Between Autonomic Nervous System and Rheumatoid Arthritis: From Bench to Bedside. Front Med (Lausanne). 2020;7:589079-.
94. Bortoluzzi A, Silvagni E, Furini F, Piga M, Govoni M. Peripheral nervous system involvement in systemic lupus erythematosus: a review of the evidence. Clinical and experimental rheumatology. 2019;37(1):146-55.
95. Stojanovich L. Autonomic dysfunction in autoimmune rheumatic disease. Autoimmun Rev. 2009;8(7):569-72.
96. Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2016;113(29):8284-9.
97. Genovese MC, Gaylis NB, Sikes D, Kivitz A, Lewis Horowitz D, Peterfy C, et al. Safety and efficacy of neurostimulation with a miniaturised vagus nerve stimulation device in patients with multidrug-refractory rheumatoid arthritis: a two-stage multicentre, randomised pilot study. The Lancet Rheumatology. 2020;2(9):e527-e38.
98. Thomas KS, Motivala S, Olmstead R, Irwin MR. Sleep depth and fatigue: role of cellular inflammatory activation. Brain Behav Immun. 2011;25(1):53-8.
99. Grabovac I, Haider S, Berner C, Lamprecht T, Fenzl KH, Erlacher L, et al. Sleep Quality in Patients with Rheumatoid Arthritis and Associations with Pain, Disability, Disease Duration, and Activity. Journal of clinical medicine. 2018;7(10).
100. Sariyildiz MA, Batmaz I, Bozkurt M, Bez Y, Cetincakmak MG, Yazmalar L, et al. Sleep quality in rheumatoid arthritis: relationship between the disease severity, depression, functional status and the quality of life. Journal of clinical medicine research. 2014;6(1):44-52.
101. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep medicine reviews. 2008;12(3):197-210.
102. Lewis I, Hackett KL, Ng W-F, Ellis J, Newton JL. A two-phase cohort study of the sleep phenotype within primary Sjögren's syndrome and its clinical correlates. Clinical and experimental rheumatology. 2019;37 Suppl 118(3):78-82.
103. Irwin MR. Sleep and inflammation: partners in sickness and in health. Nature reviews Immunology. 2019;19(11):702-15.
104. Palagini L, Tani C, Mauri M, Carli L, Vagnani S, Bombardieri S, et al. Sleep disorders and systemic lupus erythematosus. Lupus. 2014;23(2):115-23.
105. Hackett KL, Gotts ZM, Ellis J, Deary V, Rapley T, Ng WF, et al. An investigation into the prevalence of sleep disturbances in primary Sjögren's syndrome: a systematic review of the literature. Rheumatology (Oxford, England). 2017;56(4):570-80.
106. Guyon A, Balbo M, Morselli LL, Tasali E, Leproult R, L'Hermite-Balériaux M, et al. Adverse effects of two nights of sleep restriction on the hypothalamic-pituitary-adrenal axis in healthy men. The Journal of clinical endocrinology and metabolism. 2014;99(8):2861-8.
107. Reinisch T, Hinz H. In Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine. Ganten, D. and Ruckpaul, K. Springer. 2006;9:919.
108. Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine. Nitrosative Stress. Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine. Berlin, Heidelberg: Springer Berlin Heidelberg; 2006. p. 1293-.
109. Avalos I, Chung CP, Oeser A, Milne GL, Morrow JD, Gebretsadik T, et al. Oxidative stress in systemic lupus erythematosus: relationship to disease activity and symptoms. Lupus. 2007;16(3):195-200.
110. Shah D, Kiran R, Wanchu A, Bhatnagar A. Oxidative stress in systemic lupus erythematosus: relationship to Th1 cytokine and disease activity. Immunology letters. 2010;129(1):7-12.
111. Powers SK, Ji LL, Kavazis AN, Jackson MJ. Reactive oxygen species: impact on skeletal muscle. Comprehensive Physiology. 2011;1(2):941-69.
112. Novelli GP, Bracciotti G, Falsini S. Spin-trappers and vitamin E prolong endurance to muscle fatigue in mice. Free radical biology & medicine. 1990;8(1):9-13.
113. Shindoh C, DiMarco A, Thomas A, Manubay P, Supinski G. Effect of N-acetylcysteine on diaphragm fatigue. Journal of applied physiology (Bethesda, Md : 1985). 1990;68(5):2107-13.

114. Dassouki T, Benatti FB, Pinto AJ, Roschel H, Lima FR, Augusto K, et al. Objectively measured physical activity and its influence on physical capacity and clinical parameters in patients with primary Sjögren's syndrome. Lupus. 2017;26(7):690-7.
115. Miyamoto ST, Valim V, Carletti L, Ng WF, Perez AJ, Lendrem DW, et al. Supervised walking improves cardiorespiratory fitness, exercise tolerance, and fatigue in women with primary Sjogren's syndrome: a randomized-controlled trial. Rheumatol Int. 2019;39(2):227-38.
116. James K, Lendrem D, Mitchell S, Hindmarsh V, Bowman S, Price EJ, et al. 205. The UK Primary Sjögren's Syndrome Registry (UKPSSR): A Valuable Resource for Future Sjögren's Syndrom Research. Rheumatology. 2014;53(suppl_1):i136-i.
117. Ng W-F, Miller A, Bowman SJ, Price EJ, Kitas GD, Pease C, et al. Physical activity but not sedentary activity is reduced in primary Sjögren's syndrome. Rheumatology international. 2017;37(4):623-31.
118. Wouters EJM, van Leeuwen N, Bossema ER, Kruize AA, Bootsma H, Bijlsma JWJ, et al. Physical activity and physical activity cognitions are potential factors maintaining fatigue in patients with primary Sjögren's syndrome. Annals of the rheumatic diseases. 2012;71(5):668-73.
119. Keyser RE, Rus V, Cade WT, Kalappa N, Flores RH, Handwerger BS. Evidence for aerobic insufficiency in women with systemic Lupus erythematosus. Arthritis and rheumatism. 2003;49(1):16-22.
120. Metsios GS, Koutedakis Y, Veldhuijzen van Zanten JJ, Stavropoulos-Kalinoglou A, Vitalis P, Duda JL, et al. Cardiorespiratory fitness levels and their association with cardiovascular profile in patients with rheumatoid arthritis: a cross-sectional study. Rheumatology (Oxford, England). 2015;54(12):2215-20.
121. Løppenthin K, Esbensen BA, Jennum P, Østergaard M, Tolver A, Thomsen T, et al. Sleep quality and correlates of poor sleep in patients with rheumatoid arthritis. Clinical rheumatology. 2015;34(12):2029-39.
122. Rongen-van Dartel SA, Repping-Wuts H, Flendrie M, Bleijenberg G, Metsios GS, van den Hout WB, et al. Effect of Aerobic Exercise Training on Fatigue in Rheumatoid Arthritis: A Meta-Analysis. Arthritis care & research. 2015;67(8):1054-62.
123. Cramp F. The role of non-pharmacological interventions in the management of rheumatoid-arthritis-related fatigue. Rheumatology (Oxford, England). 2019;58(Supplement_5):v22-v8.
124. Cramp F, Hewlett S, Almeida C, Kirwan JR, Choy EH, Chalder T, et al. Non-pharmacological interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev. 2013(8):Cd008322.
125. ROBB-NICHOLSON LC, DALTROY L, EATON H, GALL V, WRIGHT E, Hartley L, et al. Effects of aerobic conditioning in lupus fatigue: a pilot study. Rheumatology. 1989;28(6):500-5.
126. Tench C, McCarthy J, McCurdie I, White P, D'Cruz D. Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. Rheumatology. 2003;42(9):1050-4.
127. Tournadre A, Pereira B, Gossec L, Soubrier M, Dougados M. Impact of comorbidities on fatigue in rheumatoid arthritis patients: Results from a nurse-led program for comorbidities management (COMEDRA). Joint bone spine. 2019;86(1):55-60.
128. Feldthusen C, Grimby-Ekman A, Forsblad-d'Elia H, Jacobsson L, Mannerkorpi K. Explanatory factors and predictors of fatigue in persons with rheumatoid arthritis: A longitudinal study. Journal of rehabilitation medicine. 2016;48(5):469-76.
129. Katz P, Margaretten M, Trupin L, Schmajuk G, Yazdany J, Yelin E. Role of Sleep Disturbance, Depression, Obesity, and Physical Inactivity in Fatigue in Rheumatoid Arthritis. Arthritis care & research. 2016;68(1):81-90.
130. Chaiamnuay S, Bertoli AM, Fernández M, Apte M, Vilá LM, Reveille JD, et al. The impact of increased body mass index on systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA XLVI) [corrected]. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases. 2007;13(3):128-33.
131. Oeser A, Chung CP, Asanuma Y, Avalos I, Stein CM. Obesity is an independent contributor to functional capacity and inflammation in systemic lupus erythematosus. Arthritis and rheumatism. 2005;52(11):3651-9.
132. Pajoutan M, Ghesmaty Sangachin M, Cavuoto LA. Central and peripheral fatigue development in the shoulder muscle with obesity during an isometric endurance task. BMC Musculoskelet Disord. 2017;18(1):314.
133. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nature medicine. 2012;18(3):363-74.
134. Andonian BJ, Huffman KM. Skeletal muscle disease in rheumatoid arthritis: the center of cardiometabolic comorbidities? Current opinion in rheumatology. 2020;32(3):297-306.
135. An HJ, Tizaoui K, Terrazzino S, Cargnin S, Lee KH, Nam SW, et al. Sarcopenia in Autoimmune and Rheumatic Diseases: A Comprehensive Review. International journal of molecular sciences. 2020;21(16).

136. Lindvall B, Bengtsson A, Ernerudh J, Eriksson P. Subclinical myositis is common in primary Sjögren's syndrome and is not related to muscle pain. The Journal of rheumatology. 2002;29(4):717-25.
137. Baker JF, Von Feldt J, Mostoufi-Moab S, Noaiseh G, Taratuta E, Kim W, et al. Deficits in muscle mass, muscle density, and modified associations with fat in rheumatoid arthritis. Arthritis care & research. 2014;66(11):1612-8.
138. Caimmi C, Caramaschi P, Venturini A, Bertoldo E, Vantaggiato E, Viapiana O, et al. Malnutrition and sarcopenia in a large cohort of patients with systemic sclerosis. Clinical rheumatology. 2018;37(4):987-97.
139. Hollingsworth KG, Newton JL, Robinson L, Taylor R, Blamire AM, Jones DE. Loss of capacity to recover from acidosis in repeat exercise is strongly associated with fatigue in primary biliary cirrhosis. Journal of hepatology. 2010;53(1):155-61.
140. Hollingsworth KG, Newton JL, Taylor R, McDonald C, Palmer JM, Blamire AM, et al. Pilot study of peripheral muscle function in primary biliary cirrhosis: potential implications for fatigue pathogenesis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2008;6(9):1041-8.
141. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology (Oxford, England). 2013;52(12):2136-48.
142. Gold SM, Köhler-Forsberg O, Moss-Morris R, Mehnert A, Miranda JJ, Bullinger M, et al. Comorbid depression in medical diseases. Nature reviews Disease primers. 2020;6(1):69.
143. Norheim KB, Jonsson G, Omdal R. Biological mechanisms of chronic fatigue. Rheumatology (Oxford, England). 2011;50(6):1009-18.
144. Hackett KL, Davies K, Tarn J, Bragg R, Hargreaves B, Miyamoto S, et al. Pain and depression are associated with both physical and mental fatigue independently of comorbidities and medications in primary Sjogren's syndrome. RMD Open. 2019;5(1):e000885.
145. Wilson N, Lee JJ, Bei B. Postpartum fatigue and depression: A systematic review and meta-analysis. J Affect Disord. 2019;246:224-33.
146. World Health Organisation (WHO). ICD-10 classification of mental and behavioural disorders 2016 [5th:[
147. Nerurkar L, Siebert S, McInnes IB, Cavanagh J. Rheumatoid arthritis and depression: an inflammatory perspective. Lancet Psychiatry. 2019;6(2):164-73.
148. Bårdsen K, Nilsen MM, Kvaløy JT, Norheim KB, Jonsson G, Omdal R. Heat shock proteins and chronic fatigue in primary Sjögren's syndrome. Innate immunity. 2016;22(3):162-7.
149. Mondelli V, Vernon AC. From early adversities to immune activation in psychiatric disorders: the role of the sympathetic nervous system. Clinical and experimental immunology. 2019;197(3):319-28.
150. Rossi S, Studer V, Motta C, Polidoro S, Perugini J, Macchiarulo G, et al. Neuroinflammation drives anxiety and depression in relapsing-remitting multiple sclerosis. Neurology. 2017;89(13):1338-47.
151. Omdal R, Mellgren SI, Norheim KB. Pain and fatigue in primary Sjögren's syndrome. Rheumatology (Oxford, England). 2019.
152. Nichilatti LP, Fernandes JM, Marques CP. Physiopathology of pain in systemic erythematosus lupus. Lupus. 2020;29(7):721-6.
153. Morgan C, Bland AR, Maker C, Dunnage J, Bruce IN. Individuals living with lupus: findings from the LUPUS UK Members Survey 2014. Lupus. 2018;27(4):681-7.
154. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. Arthritis care & research. 2010;62(5):647-56.
155. Bower JE. Behavioral symptoms in patients with breast cancer and survivors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(5):768-77.
156. Camacho EM, Verstappen SM, Chipping J, Symmons DP. Learned helplessness predicts functional disability, pain and fatigue in patients with recent-onset inflammatory polyarthritis. Rheumatology (Oxford, England). 2013;52(7):1233-8.
157. Jacobsen PB, Andrykowski MA, Thors CL. Relationship of catastrophizing to fatigue among women receiving treatment for breast cancer. Journal of consulting and clinical psychology. 2004;72(2):355-61.
158. Segal BM, Pogatchnik B, Rhodus N, Sivils KM, McElvain G, Solid CA. Pain in primary Sjögren's syndrome: the role of catastrophizing and negative illness perceptions. Scandinavian journal of rheumatology. 2014;43(3):234-41.
159. Hewlett S, Almeida C, Ambler N, Blair PS, Choy EH, Dures E, et al. Reducing arthritis fatigue impact: two-year randomised controlled trial of cognitive behavioural approaches by rheumatology teams (RAFT). Annals of the rheumatic diseases. 2019;78(4):465-72.

160. Dures E, Kitchen K, Almeida C, Ambler N, Cliss A, Hammond A, et al. "They didn't tell us, they made us work it out ourselves": patient perspectives of a cognitive-behavioral program for rheumatoid arthritis fatigue. Arthritis care & research. 2012;64(4):494-501.
161. Sanada K, Montero-Marin J, Barceló-Soler A, Ikuse D, Ota M, Hirata A, et al. Effects of Mindfulness-Based Interventions on Biomarkers and Low-Grade Inflammation in Patients with Psychiatric Disorders: A Meta-Analytic Review. International journal of molecular sciences. 2020;21(7).
162. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nature reviews Clinical oncology. 2014;11(10):597-609.
163. Nadarajah M, Goh HT. Post-stroke fatigue: a review on prevalence, correlates, measurement, and management. Topics in stroke rehabilitation. 2015;22(3):208-20.
164. Sterling P. Allostasis: a model of predictive regulation. Physiology & behavior. 2012;106(1):5-15.
165. Zautra AJ, Fasman R, Parish BP, Davis MC. Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Pain. 2007;128(1-2):128-35.
166. Drewes AM. Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. Rheumatology (Oxford, England). 1999;38(11):1035-8.