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Impact of fatigue on rheumatic diseases

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A B S T R A C T

Fatigue is a common, disabling, and difficult-to-manage problem in rheumatic diseases. The concept of fatigue is difficult to define. No clear and widely accepted definition of fatigue is available. The symptoms of fatigue are defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases the ability to function and carry out daily activities. Prevalence estimates of fatigue within musculoskeletal diseases vary considerably (35%−82%). In this review, we present data about the role of fatigue for the patients' quality of life, tools for diagnosing fatigue, factors contributing to fatigue like disease activity and psychological factors, and some experimental studies to verify the biological background of fatigue. Management of fatigue including pharmacological and non-pharmacological treatment is also part of this publication. Overall data are scarce for fatigue in rheumatic diseases, and further studies are warranted to identify the role of biological mechanism such as inflammation, hormonal changes, and autonomic nervous system in the pathogenesis of fatigue.
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Definition and diagnostic tools for fatigue

Fatigue is a common, disabling, and difficult-to-manage problem in rheumatic diseases. The concept of fatigue is difficult to define. No clear and widely accepted definition of fatigue is available. The symptoms of fatigue are defined as an overwhelming, debilitating, and sustained sense of

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exhaustion that decreases the ability to function and carry out daily activities [1]. Prevalence estimates of fatigue within musculoskeletal diseases vary considerably (35%–82%) [2].

Most humans have experienced acute fatigue in relation to different stressors. Acute fatigue typically decreases as the effect of the triggering factor is dwindling and a normal homeostatic balance is restored. Fatigue that persists for 6 months or more is termed chronic fatigue [3]. Fatigue severity is varying from mild to severe disturbance. For example, about 80% of patients with RA report experiencing fatigue, with 50% rating the fatigue as severe [1].

Fatigue is a subjective experience and hence, difficult to measure. A large number of instruments have been developed to measure fatigue. In this respect, criteria were developed for judging the “ideal” measure to encompass scale usability, clinical/research utility, and the robustness of psychometric properties. Twenty-two fatigue measures met the inclusion criteria and were evaluated. A further 17 measures met some of the criteria, but have not been tested beyond initial development. However, a small number of short instruments demonstrated good psychometric properties (Fatigue Severity Scale: FSS, Fatigue Impact Scale: FIS, and Brief Fatigue Inventory: BFI) and three comprehensive instruments scored similarly for the respective measurements (Fatigue Symptom Inventory: FSI, Multidimensional Assessment of Fatigue: MAF, and Multidimensional Fatigue Symptom Inventory: MFSI). Only four measures (BFI, FSS, FSI, and MAF) demonstrated the ability to detect change over time [4]. For the measurement of fatigue in rheumatic diseases, FSS und MAF have been used. FSS was developed to assess disabling fatigue in multiple sclerosis (MS) and SLE, and was published in 1989. The FSS covers physical, social, or cognitive effects of fatigue (e.g., function, work, motivation) [5]. MAF was developed to measure multiple dimensions of fatigue in adults with RA. The MAF covers 4 dimensions of fatigue: severity, distress, interference in activities of daily living (doing chores, cooking, bathing, dressing, working, visiting, sexual activity, leisure, shopping, walking and exercising), and frequency as well as change during the previous week [6]. MFSI contains psychometric qualities to assess fatigue as a 20-item self-report instrument. It covers the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [7]. The concept of ‘fatigue’ is strictly related to parameters of the setting in which fatigue is measured. Therefore, it is mandatory to provide a definition of fatigue and the modalities of its use. Over the years, other scales to measure fatigue in rheumatology were developed.

Box 1: Definition

Fatigue is a common, disabling, and difficult-to-manage problem in rheumatic diseases. The concept of fatigue is difficult to define. No clear and widely accepted definition of fatigue is available to date. The symptoms of fatigue are defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases the ability to function and carry out daily activity.

The BRAF MDQ was developed to assess the overall experience and impact of fatigue in RA. Its different dimensions comprise physical fatigue (e.g., average fatigue level over last 7 days), living with fatigue (e.g., has fatigue made it difficult to bathe or shower?), cognitive fatigue (e.g., has fatigue made it difficult to concentrate?), and emotional fatigue (e.g., has being fatigued upset you?) [8]. Lack of standardized tools for measuring fatigue limits the interpretation of data and researchers often create individual items for different studies. Therefore, the aim of the Bristol RA fatigue numerical scales (BRAF NRS) was to develop a standardized form by measuring a range of RA fatigue domains using a numerical rating scale (NRS), i.e., NRS on fatigue severity (average level of fatigue), effect (effect fatigue has had on your life), and coping (how well you have coped with fatigue) [8].

The profile of fatigue (PROF) was developed to characterize patterns of fatigue associated with primary Sjögren's syndrome (PSS). It contains somatic fatigue items for needing to rest (e.g. feeling exhausted), difficulty getting started (e.g. hard to get going), low stamina (e.g. hard to keep going), and weak muscles (e.g., feeling weak). Furthermore, it contains mental fatigue items for concentration (e.g. not thinking clearly) and memory (e.g. forgetting things) [9].

Recently, a study was published evaluating various fatigue measurements (Bristol RA Fatigue Multidimensional Questionnaire: BRAF-MDQ, revised Bristol RA Numerical Rating Scales: BRAF-NRS V2, RA Impact of Disease: RAID) in six European countries (France, Germany, The Netherlands, Spain, Sweden and the UK). A total of 1276 patients participated in the study (76% female, 25% with a disease duration < 5 years, median HAQ 1.0). Across six European countries, the BRAF-MDQ identifies the same four aspects of fatigue, and along with the RAID, shows strong factor structure and internal consistency and moderate-good construct validity. The revised BRAF-NRS V2 shows improved construct validity and replaces the original [10].

A total of 612 patients were studied to further characterize associations of fatigue with other variables within a multidimensional health assessment questionnaire (MDHAQ) in different rheumatic diseases (173 RA, 199 with OA, 146 with SLE, and 94 with FMS). Median fatigue was significantly higher in FMS (7) than in RA (4), OA (5), and SLE (5). Fatigue correlated significantly with all other MDHAQ scores with a more pronounced level in RA and SLE versus OA and FMS. In multivariate analyses, fatigue scores were explained independently by higher pain and symptom scores in RA, younger age and higher symptom score in OA; higher pain score in SLE; and none of the variables in FMS. Fatigue is common in rheumatic diseases and is strongly associated with higher pain and number of symptoms. The authors conclude that the MDHAQ provides a useful tool to assess fatigue in clinical settings [11].

To date, we test fatigue with the help of questionnaires lacking objective measurement instrument to estimate fatigue. In the clinical setting, it is quite often difficult to detach the term 'fatigue' from tiredness and task failure, which correspond to two completely distinguished forms of fatigue: one with central origin (tiredness) and another that is localized within the muscle (peripheral muscle fatigue). Electromyography (EMG) could be one of these objective recording tools to test a fatigue [12]. Peripheral muscle fatigue is related to changes in motor unit-recruitment strategies, whereas the latter is attributed to changes in membrane properties. To extensively assess fatigue and, partially, to avoid confusion among the types of fatigue described above, a number of laboratory tests have been developed; among these, there are multichannel surface electromyography (EMG) recordings. Using this approach, it is possible to estimate the motor unit location within the muscle, the decomposition of the surface EMG (sEMG) interference signal into constituent trains of motor unit action potentials (MUAPs), and the analysis of single unit properties [13]. A recent publication from 2018 [14] to assess EMG parameters of neuromuscular fatigue in knee extensors and their association with clinical, functional, and emotional features in RA patients showed no association between EMG measurements and clinical or treatment features. The EMG findings correlated with perception of fatigue, age, physical functioning and the vitality domains of SF-36, and physical activity level in this sample. These results indicate that primary muscle factors should also be considered when managing perceived fatigue in patients with RA. Another study to investigate relationships between perceived and objectively measured muscle fatigue during exhausting muscle contractions in women with FMS recorded the EMG activity in the deltoid muscle together with self-reported level of muscle fatigue. Compared with healthy controls (HC) women with FMS had shorter exhaustion times and showed fewer objective signs of muscle fatigue during an exhausting isometric shoulder abduction compared with younger HC. This indicates that perceived muscle fatigue may be of central origin and supports the notion of central nervous dysfunction as basic pathological changes in FMS [15].

Diagnostic guidelines for rheumatic diseases do not pay attention to the various patterns of fatigue in rheumatic diseases. There are three main patterns of fatigue, depending on whether the source is physical or mental: muscle weakness in patients with neuromuscular disease; asthenia related to organic disease with excessive energy expenditure, deficient energy production (e.g., endocrine disorders), or inadequate recovery; and weariness due to the impact of stress and depression on quality of life. The prevalence of each pattern in various rheumatic diseases will be the focus of further studies [16].

Background of fatigue

To date, there is no clear concept for the biological background of fatigue. Many studies have shown that the association between fatigue and inflammatory markers is not strong, and that fatigue is likely to have multicausal pathways of clinical (e.g., pain, disability) and psychosocial variables (e.g., mood, beliefs) contributing to various extent in each individual patient [17,18].

To verify the biological background of fatigue, some experimental studies were conducted. A wide array of immune, inflammatory, oxidative, and nitrosative stress (O&NS), bioenergetic, and neurophysiological abnormalities are involved in the etiopathology of autoimmune diseases and may underpin the incapacitating fatigue that accompanies these disorders. This range of abnormalities comprises increased levels of pro-inflammatory cytokines, e.g., interleukin-1 (IL-1), IL-6, tumour necrosis factor (TNF) α and interferon (IFN) α; O&NS-induced muscle fatigue; activation of the Toll-Like Receptor Cycle through pathogen-associated (PAMPs) and damage-associated (DAMPs) molecular patterns, including heat shock proteins; altered glutaminergic and dopaminergic neurotransmission; mitochondrial dysfunctions; and O&NS-induced defects in the sodium-potassium pump. Fatigue is also associated with altered activities in specific brain regions and muscle pathology, such as reductions in maximum voluntary muscle force, downregulation of the mitochondrial biogenesis master gene peroxisome proliferator-activated receptor gamma coactivator 1-alpha, a shift to glycolysis and build-up of toxic metabolites within myocytes. As such, both mental and physical fatigue, which frequently accompany immune-inflammatory and neuro-inflammatory disorders, are the consequence of complex interactions between multiple systemic and central pathways [18].

One of these publications was devoted to investigate functions of heat shock proteins (HSPs). When the innate immune system is activated, HSPs are produced to protect cells. Some extracellular HSPs appear to recognize cellular targets in the brain, and it was hypothesized that fatigue may be generated by specific HSPs signalling through neuronal or glial cells in the central nervous system. From a cohort of patients with primary Sjögren's syndrome (pSS), 20 patients with high and 20 patients with low fatigue were selected. Fatigue was evaluated with a fatigue visual analogue scale. Plasma concentrations of HSP32, HSP60, HSP72 and HSP90α were measured and analysed to determine whether there were associations with the level of fatigue. Plasma concentrations of HSP90α were significantly higher in patients with high fatigue than in those with low fatigue, and there was a tendency to higher concentrations of HSP72 in patients with high fatigue compared with patients with low fatigue. There were no differences in concentrations of HSP32 and HSP60 between the high- and low-fatigue groups. Thus, extracellular HSPs, particularly HSP90α, may signal fatigue in chronic inflammation. This supports the hypothesis that fatigue, at least in pSS, is generated by cellular defence mechanisms [19]. Furthermore, on patients with pSS whole blood samples from 133 fully phenotyped pSS patients stratified for the presence of fatigue, collected by the UK primary Sjögren's Syndrome Registry, were recruited for a whole genome microarray. The resulting data were analysed on both a gene-by-gene basis and using pre-defined groups of genes. Although no genes were individually found to be associated with fatigue, 19 metabolic pathways were enriched in the patient group with high fatigue using gene set enrichment analysis GSEA. The analysis revealed that these enrichments arose from the presence of a subset of 55 genes. Systematic analysis of gene expression data from pSS patients discordant for fatigue identified 55 genes, which are predictive of fatigue level using SVM classification. This work represents the first step in understanding the genetic background of fatigue in patients with pSS [20].

Fatigue could be associated with some psychological factors and neural mechanisms, especially mental fatigue. Mental fatigue manifests as potentially impaired cognitive function and is one of the most significant causes of accidents in modern society. Recently, it has been shown that the neural mechanisms of mental fatigue related to cognitive task performance are more complex than previously thought and that mental fatigue is not merely caused by impaired activity in task-related brain regions. There is accumulating evidence supporting the existence of mental facilitation and inhibition systems. These systems are involved in the neural mechanisms of mental fatigue, modulating the activity of task-related brain regions to regulate cognitive task performance. The model of dual regulation contributes to our understanding of neural mechanisms of mental fatigue and the regulatory mechanisms of cognitive task performance in the presence of mental fatigue [21]. A framework for mental fatigue is proposed that integrates the nucleus accumbens, orbitofrontal cortex, amygdala, insula and anterior cingulate cortex to evaluate both the potential rewards associated with performing a task and assesses the energetical demands involved in task performance. Behaviour will only proceed if this evaluation turns out favourably towards spending (additional) energy. It was proposed that this evaluation of predicted rewards and energetical costs is central to the phenomenon of mental fatigue: people will no longer be motivated to engage in task performance when energetical costs are perceived to outweigh predicted rewards [22]. Otherwise, fatigue could be also associated with hypoactivity of the hypothalamic-pituitary-adrenal axis, autonomic nervous system alterations characterized by sympathetic overactivity and low vagal tone. Further simultaneous evaluation of neuroendocrine and immune systems will help us to understand the biological background of fatigue [1,23].

Fatigue in rheumatoid arthritis (RA)

Data on the association of fatigue and disease activity in various rheumatic diseases are controversial. In this respect, the relationship with scores of disease activity in RA is uncertain [17]. Furthermore, the inflammatory activity that characterizes RA, as measured by swollen and tender joint counts, erythrocyte sedimentation rates, CRP, and the DAS28 has an inconsistent relationship with RA-related fatigue [1]. A systematic literature analysis revealed a total of 121 studies with >100 000 RA patients. A high level of fatigue was seen even in well-treated patients, demonstrating fatigue as a major problem in RA. Fatigue was found to be positively correlated with pain, CRP, DAS28, and ESR but not with swollen to tender joint count ratio, the swollen to tender joint count ratio or disease duration, with pain as the overall dominating factor. Fatigue has a substantial influence on the lives of RA patients, independent of disease duration. Disease activity is positively correlated to fatigue but does not contribute substantially after adjusting for pain. Optimal pain relief is therefore an important part of the treatment to improve fatigue in RA [24]. Moreover, biologic agents targeting inflammatory cytokines are effective against fatigue, however, not in all cases. In 6835 participants, the prevalence of severe baseline fatigue was 38.8%. Of those with severe fatigue, 70% reported clinically relevant improvement and 66% moved to the non-severe fatigue category (i.e., improvers). The mean change for improvers was three times the minimum clinically important difference for improvement. Independent baseline predictors of improvement were female sex (OR 1.3, 95% CI 1.1–1.7), not being unemployed due to ill health (OR 1.5, 95% CI 1.2–1.7), low disability (OR 1.2, 95% CI 1.001–1.5), seropositivity (OR 1.2, 95% CI 0.98–1.4), not using steroids (OR 1.2, 95% CI 1.03–1.5], no history of hypertension (OR 1.4, 95% CI 1.1–1.6)] or depression (OR 1.3, 95% CI 1.1–1.5) and good mental health (SF-36 mental health subscale > 35; OR 1.4, 95% CI 1.2, 1.7) [25]. Fatigued RA patients reported substantial improvement in their fatigue after commencing *anti*-TNF-α therapy. Therefore, despite being important in overall disease control, reductions in disease activity are not always sufficient to ameliorate fatigue; thus, other symptom-specific management approaches must be considered for those for whom fatigue does not resolve [26]. Another study presented data to examine the hypothesis that reductions in fatigue after *anti*-TNF therapy reflect changes in central, not peripheral, pain mechanisms. Six factors were identified, of which 2 met acceptance criteria (values of 2.39 and 1.14, respectively). Otherwise, following *anti*-TNF therapies, reductions in fatigue and pain appear to reflect improvements in central, rather than peripheral, inflammation. Therefore, for those seeking to treat fatigue via pain mechanisms, improvements may be maximized by the application of treatment modalities that effectively target central mechanisms [27].

Fatigue and various clinical symptoms

Fatigue is frequently associated with psychosocial factors such as depression, sleep disorder, anxiety, and coping style, which suggest that dysregulation of the body's stress systems may serve as an underlying mechanism in the maintenance of chronic fatigue. Inflammation could be a common link between fatigue, pain, and depression [28]. Otherwise, one study of RA patients demonstrated that although most patients had low levels of inflammation, 47.3% of the patients continued to report having moderate to high levels of pain and fatigue. Most of these patients had minimal signs of inflammation but high levels of fatigue, pain catastrophizing, and sleep disturbance, indicative of a chronic widespread pain (CWP) syndrome [29]. It was also shown that both sleep problems and fatigue serve as predictors for the onset of CWP. Overall, data from 1249 individuals were entered into the analyses for the 5-year follow-up and data from 791 entered into the analyses for the 18-year follow-up. Sleep problems and fatigue predicted the onset of CWP after five years independently from each other [30].

One more factor to induce/support fatigue could be low physical activity of patients with rheumatic diseases. It was shown that patients with fatigue and FMS had significantly lower physical activity scores (8834 ± 5967 and 8813 ± 5549 MET * minutes) than controls (9541 ± 5533; $p < 0.001$). Patients with fatigue had the longest sleep duration (466 ± 86 min) compared to patients with FMS and controls (450 ± 67 and 446 ± 56; $p < 0.001$). A linear association between physical activity, sleep duration, and symptom severity was found only in controls, in whom higher physical total activity scores and longer sleep duration were associated with a lower symptom severity. This study indicates that patients with fatigue or FMS sleep longer and are less physically active than controls. Both low and high levels of physical activity and short and long sleep duration are associated with higher symptom severity, suggesting the importance of patient-tailored treatment [31].

Otherwise, there is a link between fatigue and depression in patients with rheumatic diseases. In a study of patients from the Lupus BioBank of the upper Rhein, a large German-French cohort of SLE patients, 570 patients were assessed (89.1% female). Fatigue was reported by 386 patients (67.7%) compared to severe fatigue being reported by 209 patients (36.7%). In multivariate analyses, both fatigue and severe fatigue are common symptoms in SLE, and are strongly associated with depression and anxiety. Disease activity and the use of glucocorticoids were also independently associated with fatigue [32].

The prevalence of a depressive disorder in RA is estimated to be between 9.5% and 41.5% depending on the study. Depression in RA is associated with more pain, fatigue and impaired quality of life, whereby the association between depression and RA is bidirectional. Taken together, this indicates that it is necessary to detect a depression in patients with RA as early as possible in order to initiate appropriate treatment of depression in such cases [33]. Data from the tREACH study were used, comparing different treatment strategies with fatigue as secondary outcome parameter in patients with early RA. Almost half of all patients (n = 246) had high fatigue levels at baseline, decreasing slightly over time. At 12 months, 43% of patients were fatigued. While 23% of the initially fatigued patients showed lower levels of fatigue, the fatigue level had increased in 15% of the initially non-fatigued patients. The strongest predictor of fatigue was the previous fatigue levels (AUC 0.89). Higher score on the depression scale and coping with limitations was associated with developing fatigue over time in the initially non-fatigued group. Despite a strict treat-to-target strategy, fatigue remained an overall problem during the first year of treatment, and was mainly predicted by its baseline status. In subgroups, a small additional effect of depression was seen. Monitoring fatigue and depression may be important in managing fatigue [34]. This study compared symptom-related cognitions, beliefs, behaviours, quality of sleep, lack of acceptance and distress in participants with autoimmune rheumatic diseases such as RA, seronegative spondyloarthritis (SpA), and connective tissue disease (CTD), and participants with chronic fatigue syndrome (CFS) (303 participants). The CFS group was more fatigued, reported more distress and sleep disturbance leading to worse social adjustment than the ARD group after adjustment for age and disease duration. After adjustment for the confounding factors, the CFS group scored higher on lack of acceptance and avoidance/resting behaviour while the autoimmune rheumatic diseases (ARD) group showed significantly higher levels of catastrophizing, damage beliefs, and symptom focussing. Similar underlying transdiagnostic processes may perpetuate fatigue in rheumatic diseases. The ARD and CFS groups showed similarities but also key differences in their responses to symptoms. Specific aspects of treatment may need to be tailored towards each group. For example, lack of acceptance and avoidance behaviour may be particularly important in perpetuating fatigue in CFS [35].

A focus on the psychological variables associated with fatigue may help to identify targets for intervention, which could enhance the treatment of fatigue. A meta-analysis to identify psychological variables related to fatigue in RA, with the overall aim of suggesting evidence-based targets for fatigue intervention in RA identified 29 studies meeting the inclusion criteria and were summarised in a narrative synthesis. A wide range of psychological variables was addressed, spanning six categories: affect and common mental disorders; RA-related cognitions; non-RA-related cognitions; personality traits; stress and coping; and social support/interpersonal relationships. The most consistent relationship was found between mood and fatigue, with low mood frequently associated with increased fatigue. Some evidence also highlighted the relationship between RA-related cognitions (such as RA self-efficacy) and fatigue, and non-RA-cognitions (such as goal ownership) and fatigue. Limited evidence was found to support the relationship between stress and coping or personality traits and fatigue, although mixed evidence was found for the relationship between social support and fatigue. The results of this review suggest that interventions for fatigue in RA may benefit from a focus upon mental health and disease-related cognitions [36].

Clinical relevance

Patients identify fatigue as an important patient-reported outcome measure [37]. Suffering patients consider management of their fatigue to be a treatment priority; however, health-care providers address it infrequently, and doctors rarely consider it a primary outcome parameter in RA treatment [1]. In addition, data on the prevalence of severe fatigue across multiple rheumatic diseases using a similar instrument are missing. In one study to provide an overview of the prevalence of severe fatigue across a broad range of rheumatic diseases online questionnaires were filled out by 6120 patients (88% female, mean age 47; international cohort) encompassing 30 different rheumatic diseases. Fatigue was measured with the Short Form 36 vitality scale (SF 36). This scale is a multi-dimensional, general health status patient-reported outcome measure (PROM) containing subscales for eight domains. The questionnaire was developed to measure vitality, conceptualized as a single continuum from energy to fatigue, in healthy and clinical populations [38]. Severe fatigue was present in 41%–57% of patients with a single inflammatory rheumatic disease such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), Sjögren's syndrome (pSS), psoriatic arthritis, and scleroderma (SSc). Severe fatigue was least prevalent in patients with osteoarthritis (35%) and most prevalent in patients with fibromyalgia syndrome (82%). In logistic regression analysis, severe fatigue was associated with having fibromyalgia syndrome (FMS), having multiple rheumatic diseases without FMS, younger age, lower education, and population (French: highest prevalence; Dutch: lowest prevalence) [2].

A meta-analysis encompassing a systematic literature search in 2017 could identify eight qualitative articles including 212 people with RA (69% women) and aged between 20 and 83 years to verify the role of fatigue for the patients and their quality of life. The overall result was summarised in the quote ‘A vicious circle of an unpredictable symptom’. In addition, the analysis derived four subthemes: ‘being alone with fatigue’; ‘time as a challenge’; ‘language as a tool for increased understanding’ and ‘strategies to manage fatigue’. Fatigue affects all areas of everyday life for people with RA. They strive to plan and prioritise, pace, relax and rest. Furthermore, they try to make use of a variety of words and metaphors to explain to other people that they experience that RA-related fatigue is different from normal tiredness. Despite this, people with RA-related fatigue experience feeling alone with their symptom and they develop their own strategies to manage fatigue in their everyday life. The unpredictability of RA-related fatigue is dominant, pervasive and is experienced as a vicious circle, which can be described in relation to its physical, cognitive, emotional and social impact. It is important for health-care professionals to acknowledge and address the impact of fatigue on the patients' everyday lives. Support from health-care professionals to manage fatigue and develop strategies to increase physical activity and maintain work is important for people with RA-related fatigue [39].

Analysis of monthly variation of fatigue showed statistically significant variation in fatigue ratings concerning VAS fatigue score ($p < 0.01$) as well as the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) total score and Living, Cognition ($p < 0.001$), and Physical ($p < 0.05$) sub-scores, but not the BRAF-MDQ Emotional sub-score. The greatest variations were seen from January to September, with higher fatigue ratings in January. The changes in VAS fatigue scores over time were considered to be of clinical importance. Analysis of seasonal variation revealed a statistically significant seasonal variation in fatigue levels, with higher fatigue values during the winter as measured by VAS fatigue score ($p < 0.01$) as well as BRAF-MDQ total score ($p < 0.01$) and Physical and Living sub-scores (both $p < 0.01$). The greatest variation was seen between winter and autumn for VAS fatigue and between winter and summer for BRAF-MDQ total score and Physical and Living sub-scores. There were no statistical differences in fatigue levels, monthly or seasonal, between sexes or age groups [40].

The European Scleroderma Observational Study showed the burden of disability in early dcSSc that worsening HAQ-DI over 12 months was strongly associated with increasing degree of skin thickening mRSS ($\rho = 0.40$, $P < 0.0001$), decreasing hand function ($\rho = 0.57$, $P < 0.0001$) and increasing fatigue ($\rho = -0.53$, $P < 0.0001$) [41]. Fatigue is associated with psychosocial factors (depression, pain and sleep disorders) and clinical manifestations of the disease (pulmonary and gastrointestinal involvement). The study from Rehabilitation Centres located in Greece to assess the relationship between fatigue and quality of life among 179 patients with osteoarthritis and RA utilised the Fatigue Assessment Scale and the Missoula-VITAS Quality of Life Index-15 (MVQoLI-15). The analysis did not reveal statistically significant correlation between fatigue and quality of life neither in the total sample nor among patients with osteoarthritis ($r = -0.159$; $p = 0.126$) or RA. However, there was a statistically significant relationship between some aspects of fatigue and dimensions of quality of life. Osteoarthritis patients had statistically significant lower MVQoLI-15 score than RA patients (13.73 ± 1.811 vs 14.61 ± 1.734) and lower FAS score than RA (26.14 ± 3.668 vs 29.94 ± 3.377) (p-value < 0.001). The finding that different aspects of fatigue may affect various dimensions of quality of life may help health-care professionals by proposing the early treatment of fatigue in order to gain benefits for quality of life [42]. In multivariate analyses, illness perception accounted for 51% of variance in physical scales of quality of life. A stronger belief in the consequences of RA (consequences, $\beta = -0.33$) and a stronger belief in repeated disease recurrence (timeline cyclical, $\beta = -0.31$) were significantly associated with physical scale of quality of life in the fully adjusted model. Illness perception accounted for 45% of variance in the mental scale quality of life. Emotional representation ($\beta = -0.27$) and fatigue ($\beta = -0.36$) were significantly associated with the mental scale quality of life in the fully adjusted model [43]. Otherwise, it was shown that fatigue could be an independent factor that predict work disability in patients with rheumatic disease. One study aimed to test the hypothesis that the prevalent symptom of fatigue longitudinally predicts work disability among RA and AS patients commencing etanercept. Two observational studies comprising 1747 RA and 1003 AS patients, respectively, were analysed who started a therapy with etanercept. For AS, fatigue was significantly associated with presenteeism (linear mixed model coefficient 3.75, 95% confidence interval (CI) 2.14 to 5.36) and activity impairment (2.62, 1.26 to 3.98), but not with work productivity loss (1.81, −0.40 to 4.02) or absenteeism (generalised linear mixed model odds ratio (OR) 1.18, 95% CI 0.92 to 1.51). In RA, fatigue was associated with presenteeism (coefficient 3.44, 95% CI 2.17 to 4.70), activity impairment (1.52, 0.79 to 2.26), work productivity loss (4.16, 2.47 to 5.85), and absenteeism (OR 1.23, 95% CI 1.02 to 1.49). Among patients beginning etanercept therapy, fatigue has a significant and independent effect on absenteeism, presenteeism, productivity loss, and activity impairment for RA patients and a significant but dimension-selective effect on work disability among AS patients [44].

The patients' perspective

Patients with rheumatic diseases express a proper interest to test fatigue. A study on 22 participants with experience of rheumatic disease-related fatigue attended a focus group and/or an individual interview. Participants were asked about their experience completing a daily diary questionnaire. While the patients were motivated to complete this questionnaire, they emphasized the importance to have clear instructions, questionnaire items and response scales. Addressing these concerns will ensure the reliability and validity of quantitative diary data [45].

Furthermore, patients with rheumatic diseases would like to receive more information about fatigue in health care units to understand this symptom. In a small study, patients with rheumatic disease and fatigue were interviewed before and after receiving a fatigue booklet. Patients and professionals with relevant interests participated in a focus group. Interviewees consistently reported that fatigue made life more challenging, and none had previously received any support to manage it. Reflecting on the booklet, most said that it had made a difference to how they thought about fatigue, and that this had been valuable. Around half of the participants also said that it had affected, or would affect, how they managed fatigue. No participant reported any impact on fatigue itself. Comments from interviewees and focus group members alike suggested that the research process might have contributed to the changes in thought and behaviour reported. This study indicated that written information can make a difference to how people think about fatigue and may prompt behaviour change.

However, the context appeared to be important: it seems likely that the research process played a part and that the impact of the booklet may have been less if read in isolation. Aspects of the research appearing to facilitate impact could be integrated into routine care, providing a pragmatic (relatively low-cost) response to an unmet need [46].

In conclusion, one out of every two patients with a rheumatic disease is severely fatigued. As severe fatigue is detrimental to the patient, due to low quality of life, and the society at large, unravelling the underlying mechanisms of fatigue and developing optimal treatment should be top priorities in rheumatologic research and practice [2].

Treatment

Clinically relevant fatigue is common in patients with rheumatic diseases. However, the management of fatigue is rather challenging and it should address the multifactorial nature of fatigue. Recent publications show that fatigue can be improved by treating the rheumatic disease with traditional and biological anti-rheumatic drugs besides various non-pharmacological approaches (physical activity, psychosocial interventions). Age does not appear to be of major importance for fatigue, and similar strategies for treating fatigue apply to all age groups, including the elderly [37].

In one study, it was shown that significant reduction in fatigue scores and disease activity were observed in patients with RA from baseline to 6 months after treatment with adalimumab. A predictive regression model of fatigue severity was proposed and was found to be significant, with RA disease activity as the most significant predictor of fatigue severity [47]. Data from an open-label rituximab study in 28 pSS patients showed that at baseline 24 (86%) patients rated physical fatigue as the complaint most eligible for improvement (median importance of 10), followed by pain, dryness, and mental fatigue. After rituximab treatment, physical fatigue showed a maximum improvement of 2.5 points and 31% in median values at group level, and 10 (36%) patients reached a physical fatigue score < 5 representing patient-acceptable symptom state (PASS). Further analysis over time revealed that physical fatigue was significantly associated with absolute number of B cells, dryness and mental fatigue, but not with ESSDAI, IgG levels and IgM-RF. Physical fatigue characterizes patient experience of pSS. Rituximab treatment resulted in significant improvement of patient-reported symptoms. However, the large majority of patients still experienced physical fatigue at an unsatisfactory level, above the cut-off value for PASS [48]. A multicentre prospective study to assess predictive factors of improvement in fatigue in RA patients requiring initiation or change of biologic therapy included 99 patients. FACIT scores at baseline revealed frequently reported fatigue (89% of patients), high prevalence of sleep disorders (95% of patients) and depression (67% of patients). Improvement of fatigue, sleep quality and depression was observed in 58.6%, 26.3% and 34.3% of patients, respectively. Significant factors associated with an improvement in fatigue at 3 months were an elevated sedimentation rate at baseline (OR = 5.7 [2.0–16.0], $p = 0.001$) and a favourable EULAR response at three months (OR = 4.8 [1.6–14.8], $p = 0.006$). Furthermore, a higher number of swollen joints (>5) at baseline (OR = 0.3 [0.1–0.8]) and the use of psychotropic drugs (OR = 0.2 [0.04–0.9]) were predictive of an absence of improvement in fatigue. No significant association with the improvement in sleep disorders could be demonstrated. The authors conclude that fatigue in RA is improved by effective treatment via decreasing disease activity [49].

A meta-analysis of randomised controlled trials reporting fatigue identified 32 studies in rheumatic diseases. Twenty studies evaluated five anti-tumour necrosis factor (*anti*-TNF) agents (adalimumab, certolizumab, etanercept, golimumab and infliximab), and 12 studies focused on five non-*anti*-TNF biologic agents (abatacept, canakinumab, rituximab, tocilizumab and an anti-interferon gamma monoclonal antibody). In total, these studies included 9946 participants in the intervention groups and 4682 participants in the control groups. The studies used five different instruments to assess fatigue in these studies: the Functional Assessment of Chronic Illness Therapy Fatigue Domain (FACIT-F), Short Form-36 Vitality Domain (SF-36 VT), Visual Analogue Scale (VAS) (0–100 or 0 to 10) and the Numerical Rating Scale (NRS). Overall treatment by biologic agents led to statistically significant reduction in fatigue with a standardized mean difference of −0.43 (95% confidence interval (CI) −0.38 to −0.49). This equates to a difference of 6.45 units (95% CI 5.7 to 7.35) of the FACIT-F score (range 0–52). Both types of biologic agents achieved a similar level of improvement. For *anti*-TNF agents, this stood at

−0.42 (95% CI -0.35 to −0.49), equivalent to 6.3 units (95% CI 5.3 to 7.4) on the FACIT-F score; and for non-*anti*-TNF biologics, it was −0.46 (95% CI -0.39 to −0.53), equivalent to 6.9 units (95% CI 5.85 to 7.95) on the FACIT-F score. In most studies, the double-blind period was 24 weeks or less. No study assessed long-term changes in fatigue. Treatment with biologic interventions in patients with active RA can lead to a small to moderate improvement in fatigue. The magnitude of improvement is similar for *anti*-TNF and non-*anti*-TNF biologics [50]. However, it is unclear whether the improvement results from a direct action of the biologics on fatigue or indirectly through reduction in inflammation, disease activity or some other mechanism [51].

Serotonin reuptake inhibitors (SSRIs) may be valuable in patients with fatigue not only because they improve the mental status, but also via their recently demonstrated anti-inflammatory effects [52]. Fatigue was assessed as a secondary outcome parameter in a 2-phase, 24-week study in outpatients with American College of Rheumatology-defined FMS. Patients were randomized to duloxetine 60−120 mg/d (N = 263) or placebo (N = 267) for the 12-week acute phase. At Week 12, all placebo-treated patients were switched to double blind treatment with duloxetine for the extension phase. At Week 12, duloxetine versus placebo significantly (all p < .05) reduced ratings on each MFI scale, pain, anxiety, depressed mood, and stiffness. Improvement in ratings of being bothered by sleep difficulties was significant only at week 4 and 8. At week 24, mean improvements in all measures was maintained for patients who received duloxetine for the entirely 24 weeks (n = 176). Placebo-treated patients switching to duloxetine (n = 187) had a significant within-group improvement in physical fatigue (Weeks 16, 20, and 24); general fatigue (Weeks 20 and 24); mental fatigue (Week 20); and reduced activity (Weeks 20 and 24). These patients also experienced significant within-group improvement in pain (Brief Pain Inventory), anxiety, depressed mood, bothered by sleep difficulties, and stiffness. Treatment with duloxetine significantly improved multiple dimensions of fatigue in FMS patients and improvement was maintained for up to 24 weeks [53].

To test the role of non-pharmacological therapy on fatigue the effect of a pedometer-based intervention on increasing physical activity and decreasing fatigue among individuals with RA was tested. A total of 96 individuals participated. Both intervention groups significantly increased steps (+1441 [P = 0.004] for pedometer and step-monitoring diary (PED) and +1656 [P = 0.001] for pedometer and diary plus step targets (PED+), and the education (EDUC) group decreased steps (−747 [P = 0.14]) (group-by-time interaction P = 0.0025). Mean changes in fatigue scores from baseline to week 21 were −1.6 (with-group P = 0.26), −3.2 (P = 0.02), and −4.8 (P = 0.0002) for EDUC, PED, and PED + groups, respectively. Function and self-reported disease activity also improved in the PED and PED + groups. Provision of pedometers, with and without providing step targets, was successful in increasing activity levels and decreasing fatigue in this sample of individuals with RA [54]. In another assessor-blinded randomized controlled multicentre trial 130 women with FMS (age 22−64 years) were investigated to examine the effects of person-centred progressive resistance exercise compared with an active control group. The intervention was performed twice a week for 15 weeks. Outcomes were five dimensions of fatigue measured with the Multidimensional Fatigue Inventory (MFI-20). An increased improvement was found at the post-treatment examination in the resistance exercise group compared to the active control group for the MFI-20 subscale of physical fatigue (resistance group Δ −1.7, SD 4.3, controls Δ 0.0, SD 2.7, p = 0.013) with an effect size of 0.33. Sleep efficiency was the strongest predictor of improvement in the MFI-20 subscale general fatigue (beta = −0.54, p = 0.031, R (2) = 0.05). Participating in resistance exercise (beta = 1.90, p = 0.010) and working fewer hours per week (beta = 0.84, p = 0.005) were independent significant predictors of improvement in physical fatigue (R (2) = 0.14). Person-centred progressive resistance exercise improved physical fatigue in women with FMS when compared to an active control group [55].

Limited data suggest that aromatherapy massage and reflexology may help to reduce fatigue in RA patients. The study sample was randomly assigned to either an aromatherapy massage (n = 17), reflexology (n = 17) or the control group (n = 17). Aromatherapy massage was applied to both knees of the subjects in the first intervention group for 30 min. Reflexology was administered to both feet of subjects in the second intervention group for 40 min during weekly home visits. The control group subjects received no intervention. Pain and fatigue scores significantly decreased in the aromatherapy massage and reflexology groups compared with the control group (p < 0.05). The reflexology intervention started to decrease mean pain and fatigue scores earlier than aromatherapy massage (week 1 vs week 2 for pain, week 1 vs week 4 for fatigue) ($p < 0.05$). Aromatherapy massage and reflexology are simple and effective non-pharmacologic nursing interventions that can be used to help manage pain and fatigue in RA patients after the results have been replicated in larger studies [56].

Another study showed the efficacy of a course of high frequency (10 Hz) left-hemisphere dorsolateral prefrontal cortex (DLPFC) transcranial magnetic stimulation (TMS) in 26 patients (14 active; 12 sham) with a diagnosis of FMS. Participants underwent a double-blind stimulation protocol of daily (Monday-Friday) TMS sessions over four consecutive weeks (total of 20 sessions; 75 × 4-s 10 Hz trains at 120% resting motor threshold). Assessments were conducted at baseline, 4 weeks and at 1-month follow-up. It was found that compared to sham treatment group, patients in the active group had significantly greater improvement in the physical fatigue ($p = 0.045$) and general fatigue ($p = 0.023$) scales of the Multidimensional Fatigue Inventory-20 at the 1 month follow-up. In a responder analysis, we also found the active group was significantly more likely (2.84 times) to achieve a minimum 30% improvement in pain intensity ratings. ($p = 0.024$). High-frequency TMS applied daily for 4 weeks to the left DLPFC induces significant relief from fatigue and a greater chance of clinically meaningful improvement in pain intensity in patients with fibromyalgia [57].

Cognitive behavioural therapy (CBT) addresses links between thoughts, feelings, and behaviours and uses cognitive restructuring to facilitate behaviour changes. CBT has shown effect in patients with RA and fatigue group [58]. In a randomized controlled trial, patients who received CBT had better scores of fatigue impact after 18 weeks when using both multi-dimensional assessment of fatigue (MAF) and VAS, with an effect size of 0.59 for MAF and 0.77 for VAS, which is probably clinically relevant. The CBT intervention focused on thoughts, feelings, behaviours, personal interactions, stressors, and issues that could be expected to have an impact on fatigue. The authors of the study thus argue that the results support the theory that complex interactions between disease, personal context, cognition, fatigue, and fatigue impact explained the health benefit in the CBT group [59]. In another multicentre, 2-year randomised controlled trial, RAFT (Reducing Arthritis Fatigue: clinical Teams using CB approaches including seven sessions, co-delivered by pairs of trained rheumatology occupational therapists/nurses) for 308 RA patients improved fatigue impact. At 26 weeks, the adjusted difference between arms for fatigue impact change favoured RAFT (Bristol RA Fatigue Effect Numerical Rating Scale (BRAF-NRS 0–10) Effect −0.59, 95% CI -1.11 to −0.06), BRAF Multidimensional Questionnaire (MDQ) Total −3.42 (95% CI -6.44 to −0.39), living with Fatigue −1.19 (95% CI -2.17 to −0.21), emotional fatigue −0.91 (95% CI -1.58 to −0.23); RA self-efficacy (RASE, +3.05, 95% CI 0.43 to 5.66) (14 secondary outcomes unchanged). Effects persisted at 2 years: BRAF-NRS Effect −0.49 (95% CI -0.83 to −0.14), BRAF MDQ Total −2.98 (95% CI -5.39 to −0.57), Living with Fatigue −0.93 (95% CI -1.75 to −0.10), Emotional Fatigue −0.90 (95% CI -1.44, to −0.37); BRAF-NRS Coping +0.42 (95% CI 0.08 to 0.77) (relevance of fatigue impact improvement uncertain), RAFT satisfaction: 89% scored ≥ 8/10 vs 54% controls rating usual care booklet ($p < 0.0001$). This suggests it could be beneficial in clinical practice to incorporate cognitive-behavioural approaches into patient education programs that aim to enhance self-management [60].

Box 2: Treatment of fatigue

- a rather challenging task
- reduction of disease activity (e.g. anti-rheumatic drugs)
- non-pharmacological approaches
- e.g. physical, psychosocial etc.

Summary

Fatigue is a common, disabling, and difficult-to-manage problem in rheumatic diseases. Prevalence estimates of fatigue within musculoskeletal diseases vary considerably (35%–82%) with severe fatigue being present in 41%–57% of patients with inflammatory rheumatic disease. Patients identify fatigue as an important patient reported outcome measure. Fatigue is a subjective experience and, hence, difficult to measure. A large number of instruments, mostly questionnaires, have been developed to measure fatigue. There is no clear concept of fatigue to date particularly with respect to the biological background of fatigue. Data about association of fatigue and disease activity are controversial. Many studies have shown that association between fatigue and inflammatory markers is not strong, and that fatigue is likely to have multicausal pathways of clinical variables (e.g., pain, disability) and psychosocial variables (e.g., mood, beliefs) combined in varying amounts. Moreover, biologic agents targeting inflammatory cytokines are effective in fatigue; however, they do not work in all cases. Despite achieving clinical remission, many patients with inflammatory rheumatic disease do not achieve complete remission of their fatigue, so other symptom-specific management approaches must be considered for those for whom fatigue does not resolve. Otherwise, fatigue is frequently associated with psychosocial factors, such as depression, sleep disorder, anxiety, and coping style. Management of fatigue should be based on the multifactorial nature of fatigue. Further research is necessary to identify the pathophysiological changes in fatigue to develop additional therapeutic approaches.

Practice points

Patients identify fatigue as an important patient-reported outcome measure.
Health-care professionals should acknowledge and address the impact of fatigue on the patients' everyday lives.
Health-care professionals need to test fatigue in the patients by utilising appropriate questionnaires.
Support from health professionals to manage fatigue and develop strategies to increase physical activity and maintain work ability is important for people with fatigue.
Fatigue can be improved through treatment with traditional as well as biological anti-rheumatic drugs and with non-pharmacological approaches (physical activity, psychosocial interventions).
A focus on the psychological variables associated with fatigue may help to identify targets for interventions that could enhance the treatment of fatigue (e.g. cognitive behavioural therapy)

Research agenda

New diagnostic guidelines should be developed to investigate the various patterns of fatigue in rheumatic diseases
Further studies are warranted focussing on the biological background of fatigue. As such, both mental and physical fatigue, which frequently accompany immune-inflammatory and neuroinflammatory disorders, are of major interest.
Basic and clinical research should aim at disentangling the interactions between inflammatory changes, neurobiological functions and metabolic modulation of central nervous system parameters (e.g. neurotransmitter).

Conflicts of interest

CB has received consultant fees from AbbVie, Amgen, Sanofi-Genzyme, Janssen, Pfizer, Roche, Shire, and speaker's bureau fees from AbbVie, Amgen, BMS, Sanofi-Genzyme, Janssen, Medac, MSD, Pfizer, Roche, Shire, and UCB; OS has received speaker's bureau fees from AbbVie, Pfizer, MSD, and consultant fees from MSD and Pfizer.

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