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Review

Fatigue in rheumatic diseases

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Abstract

Fatigue is a common and important problem in many diseases including rheumatologic illnesses, and it has a negative impact on health-related quality of life. Fatigue is described as having an impact on multiple aspects of a patient's life. There is a need for knowledge about causes of and treatments for fatigue to ensure that patient outcomes are improved. There are several effective treatment strategies available for fatigue including pharmacological and non-pharmacological therapies. We aim to provide an overview of fatigue in rheumatologic disorders and some recommendations on its optimal management.

Keywords: Fatigue, rheumatic disease, quality of life, inflammation

Introduction

Fatigue is a common complaint and can be described as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion (1). It has been studied in people with various medical disorders such as rheumatic or neurological disorders, malignancies, and other chronic conditions (2, 3). In population-based surveys in Britain and the United States (US), the incidence of fatigue was described to be between 6.0% and 7.5% (4, 5). A cross-sectional survey of U.S. workers found the two-week prevalence of fatigue to be 38%, with an estimated annual cost to employers exceeding 136 billion dollars in lost productive work time (6). In general, fatigue prevalence ranges from 14% to 25%, depending on demographic, psychological, and social factors in healthy adults (7, 8). In chronic conditions, fatigue is the most common disruptive and distressful symptom experienced, and it can have a devastating effect on daily functioning and overall well-being (9). The prevalence of fatigue is generally higher in women than in men (10-14). No medical or psychiatric explanation can be found in 8.5–34% of patients with fatigue (15-19). The others have one of the following conditions: major depression, panic disorders, somatization disorders, drug use (hypnotics, muscle relaxants, antidepressants, first-generation antihistamines, beta-blockers, or opioids), chronic diseases, or cancer (17, 20).

In animal models, proinflammatory cytokines, especially interleukin-1 beta (IL-1ß), induce fatigue, and animal studies demonstrate that IL-1 induces IL-6 synthesis in neurons (21, 22) and that the injection of IL-6 and IL-1ß induces fatigue in healthy individuals (23-25). Patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) receiving IL-6-blocking agents have reported significant relief from fatigue (26, 27). Other biological agents interfering with immune processes seem to have a similar effect on fatigue, such as tumor necrosis factor-alpha (TNF-α) blocking agents (24, 25, 28). The induction of fatigue by cytokine injections and relief of fatigue in RA and SLE after treatment with biological agents support the relation with the inflammatory background of the existence of fatigue. Proinflammatory cytokines can act on mood, muscle mass, cognition, and metabolic status to induce fatigue (29, 30). Inflammatory cytokines may also induce disturbance in the hypothalamic–pituitary axis, affecting the levels of corticotropin-releasing hormone and adrenocorticotropic hormone. These hormones, in turn, may influence adrenocortical hormone secretion by the adrenal glands (30).

There is evidence of immune differences between patients with chronic fatigue and healthy controls, such as reduced circulating immune complexes, reduced natural killer (NK) cell numbers, depressed NK functions, altered immunoglobulin levels, increased IL-2 levels, and altered CD4/CD8 ratios (31-35).

Biological disease-modifying antirheumatic drugs (DMARDs) such as rituximab, a chimeric anti-CD20 monoclonal antibody that leads to the depletion of B cells, and abatacept (Orencia, Bristol-Myers Squibb, New York City, United States), an inhibitor of T-cell co stimulation, interfere with the early inflammatory cascade (36-38). In a double-blind placebo-controlled trial, 30 patients with chronic fatigue syndrome randomly received rituximab (Mabthera, Roche, Basel, Switzerland) (500 mg/m^2) or saline, given twice in two weeks. There were no differences in the primary endpoint, defined as effects on the fatigue score at three

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months after the intervention. A 67% improvement was seen in the self-reported fatigue scores of those who received rituximab, and a 13% improvement was seen in those who received placebo. There were no differences in B cell levels between patients in the rituximab group who achieved a response compared with those who did not (39).

Results of studies that evaluated the effects of glucocorticosteroids on fatigue have been inconsistent. In a double-blind, randomized, placebo-controlled trial, the use of 25–30 mg/day oral hydrocortisone for 12 weeks in 70 patients with chronic fatigue syndrome showed a modest benefit at the expense of adrenal suppression (40). In another randomized cross-over trial, the use of 5–10 mg/day hydrocortisone in 32 patients with chronic fatigue improved the symptoms without additional comorbid psychiatric disorders or adrenal suppression (41).

In persistent fatigue, blunted cortisol response to stress, dysfunction of the hypothalamus–pituitary–adrenal axis, increased oxidative stress, and high oxidation and gene levels have also been reported (42-47). Another study showed that most patients with unexplained chronic fatigue present with resting sympathetic hyperactivity and reduced vagal modulation (48). Chronic fatigue disorders including RA and SLE have persistent activation of the sympathetic nerve activation and high plasma catecholamine levels (49).

The problem with fatigue evaluation is the lack of an objective marker consistently associated with fatigue. There are several scales to assess fatigue such as Profile of Mood States, Short Form 36 (SF-36), Multidimensional Assessment of Fatigue, Ordinal Scales, Visual Analog Scales, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (50).

Majority of patients with fatigue experience chronic pain. Reduced exercise capacity, autonomic nervous system dysfunction, progression over time, and poor prognosis are associated with fatigue (51). These pain complaints show a great overlap with fibromyalgia, and concomitant fibromyalgia is a clinical problem in rheumatologic diseases. Symptoms of fibromyalgia such as increased pain, physical limitations, and fatigue may be mistaken for those of several inflammatory and autoimmune rheumatologic disorders, especially during increased activity of these diseases (52). Fatigue is common and often persistent in rheumatic diseases and can have a major impact on health-related quality of life (HRQoL) (53, 54).
RA is a chronic autoimmune disorder causing inflammation, stiffness, and pain in the joints (55). Fatigue is a common symptom among patients with RA and can be associated with pain, disability, depressive mood, anxiety, sleep disturbances, and limitations in social activities (53, 56, 57). Fatigue is found in at least 40% of patients with RA (58). Fatigue in patients with RA is associated with numerous factors such as inflammation, pain, disability, and psychosocial factors (56, 59). Pain and depression are important factors associated with fatigue, and there is no association with age, disease duration, and other comorbidities (60). Randomized controlled trials suggest that anti-TNF inhibitors decrease cytokines in the pathogenesis and reduce RA-related fatigue (61). Patients with RA who have a high level of daily physical activity have less fatigue than those with a low daily physical activity (62).

SLE is a chronic, multisystem, inflammatory, and autoimmune connective tissue disorder. Fatigue is the most prevalent complaint in approximately 50–90% of patients with SLE, (63). In most cases, the cause of fatigue is unknown. In one study, patients rated fatigue worse than pain, depression, or anxiety (64). Some studies have shown an association between disease activity (i.e., cytokine and autoantibody levels, organ damage) and fatigue, whereas others have reported that fatigue is not associated with any disease markers (64-66). No laboratory measure is correlated with the levels of fatigue. The cause of SLE-related fatigue seems to be multifactorial, such as disease activity, anxiety disorders, poor sleep patterns, and low levels of exercise (67-69). Fatigue has a significant adverse influence on HRQoL of patients such as decreasing normal daily functioning, lack of concentration, and work disability (63).

Ankylosing spondylitis (AS) is a chronic and systemic inflammatory disorder primarily affecting the sacroiliac joints and spine (70). Fatigue prevalence in AS differs from 53% to 65% (71). Several reports showed a strong correlation between fatigue, pain, disease activity, and functional capacity (71-73). Anti-inflammatory drugs are very effective for controlling pain, functional disability, and a patient's global assessment, but they have a limited effect on fatigue (72). However, regular physical activity is effective in reducing fatigue (74).

Primary Sjogren's syndrome (SS) is a rheumatic autoimmune disease characterized by lymphocyte infiltration of exocrine glands leading to mucosal dryness, particularly in the eyes and mouth (75). Besides dryness of the mucosa, fatigue is the most frequently reported symptom. The prevalence of fatigue among patients with primary SS may be 65–70% (76). Sjogren's syndrome disease activity index and Sjogren's Systemic Clinical Activity Index include fatigue as well as other subjective health complaints (77, 78). In one study, baseline sicca symptoms correlated with a higher fatigue level (79). At this point, the inflammatory component in primary SS can be associated with fatigue and can nonspecifically improve exocrine function causing less fatigue. Two small double-blind, randomized studies showed that rituximab treatment is associated with fatigue improvement (80, 81).

Systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular injury and excessive fibrosis of the skin and internal organs (82). Fatigue was reported to be present in 89% and 92% of patients in Canadian and Dutch studies, respectively (83, 84). Fatigue in SSc is associated with a reduced capacity and impaired physical function. One study found that low vital capacity, affected joint and functional impairment are the main factors influencing the scores of fatigue (85). SF-36 and FACIT are the measures of fatigue in SSc, and FACIT has a higher correlation with disease characteristics than SF-36 (86).

Behcet's disease (BD) is a chronic, systemic vasculitis affecting blood vessels of different sizes and types (87). It was reported that patients with BD have high levels of fatigue (88). Responsible factors for fatigue were found to be the presence of sleep disorders, restless legs syndrome, anxiety, and a patient's and physician's impression of disease activity (89).

Vasculitis is a group of systemic diseases involving inflammation of arteries and other tissues with resulting organ and life-threatening disorders. Fatigue is the most commonly reported symptom in patients with vasculitis. The mechanisms underlying fatigue are complex and multifactorial (90). Patient-reported measures of disease activity and remission duration are significantly associated with fatigue. However, physician-derived measures of disease activity do not correlate with fatigue (90, 91). Fatigue is a dominant problem for patients and physicians during clinical assessment; the healthcare team should take time to recognize and evaluate fatigue (92).

Studies have shown that fatigue negatively impacts HRQoL. Fatigue may exacerbate pain and disability; therefore, addressing the management of fatigue may also improve a larger cluster of symptoms (9, 59). Traditionally, the clinical management of RA has been primarily focused on the management of pain and func-

tional impairment, with relatively little attention given to the management of fatigue. Patients do not discuss fatigue with their healthcare professionals because they think that nothing can be done because it is a part of the disease, and they manage fatigue by trial and error (93, 94). Several studies have also shown that patients receive insufficient information, help, and support from healthcare professionals after diagnosis (95, 96).

The management of fatigue is successful if developed by a multidisciplinary team. This approach should be continued until symptom improvement is achieved. The management includes non-pharmacological and pharmacological modalities (97). Non-pharmacological modalities always begin with patient education. However, patient education alone is not sufficient to improve clinical outcomes. Establishing community-based patient education programmes are one of several potential actions. Self-management programmes may preferably be conducted by juxtaposed peer counselors and occupational therapists (98).

A study supports that some educational programs should be developed on fatigue for rheumatologists and other healthcare professionals, and fatigue should be a part of education programmes of healthcare professionals (99). Patient education can include pacing, energy conservation, increasing physical activity, getting regular exercise, rest–activity balance, balanced diet, lifestyle moderation, stress management, time management, and sleep hygiene (97). Cognitive behavioral therapy deals with links between thoughts and feelings that may drive behaviors and uses cognitive restructuring to help patients make behavioral changes (100).

Clinical experience indicates that energy conservation techniques such as pacing or reprioritizing activities may benefit some patients (93). Pacing of activities was emphasized by participants as an important coping strategy. Adding relaxation exercises can have a positive effect on symptoms and may improve mood, quality of life, and physical functioning (101, 102). Sleep disturbance is found in 87–95% of patients with chronic fatigue syndrome reporting unrefreshing sleep (103,104). Sleep management strategies form a part of cognitive behavioral therapy (105). Energy conservation strategies such as medication, prayer, or counseling are aimed at improving mood (59, 106, 107).

Pharmacological treatments reduce but do not resolve fatigue, and associations between RA fatigue and measures of inflammation and clinical or psychological health are only moderate (108). Moreover, few studies have assessed the impact of conventional DMARDs such as leflunomide and methotrexate on fatigue. The management of fatigue with DMARDs is associated with a decrease in disease activity, which indicates that disease activity is a potentially important causal factor for fatigue (109). Evidence from clinical trials with TNF-α inhibitors suggests that improvement in disease activity is associated with improvement in fatigue (110-112). Serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, or tricyclic antidepressants could improve the symptoms of fatigue (97). Hypovitaminosis D-associated fatigue should be managed with vitamin D supplements (113).

Fatigue is a common problem and is highly prevalent in rheumatic disorders. Fatigue causes loss of labor, delay in healing, disability, and social isolation. There are lots of etiological reasons that contribute to fatigue such as oxidative stress, genetic susceptibility, and comorbidities, such as psychological distress, chronic pain, sleep disturbance, obesity, etc. In several aspects, proinflammatory cytokines are also released parallel to fatigue. After the treatment of RA with biological DMARDs, relief of fatigue supports this condition. There are lots of treatment strategies for fatigue. It should be considered with patients' health status and their cultural background. Pharmacological and/or non-pharmacological therapies can reduce this disability symptom and can improve patients' health.

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