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Editorial

Fatigue in rheumatoid arthritis

Fatigue is a common symptom in many rheumatic diseases, including RA. However, until recently healthcare professionals and researchers had not recognized its clinical significance and its impact on patients' lives. A turning point came in 2002, at the Patient Perspective Workshop of the OMERACT meeting, when patients highlighted the importance of fatigue [1]. This led to the recommendation by OMERACT in 2006 that fatigue is included as a core outcome measure in clinical trials of RA treatments [2]. The process by which the rheumatology community has come to recognize and focus on fatigue is an example of the value of patient involvement in setting research priorities. This awareness of fatigue as a patient priority has led many researchers over the last decade to work on better understanding the causes, assessment and management of fatigue.

Qualitative research has provided insight into the nature of RA-related fatigue. Patients have described it as a complex and multidimensional symptom that can be overwhelming, unearned and unpredictable [3]. It can include physical fatigue (e.g. levels of physical energy), cognitive fatigue (e.g. concentration and clarity of thought), living with fatigue (e.g. ability to carry out activities of daily living and social activities) and emotional fatigue (e.g. feelings of distress or upset) [4]. Quantitative research has established that fatigue is highly prevalent in RA, with levels similar to those in chronic fatigue syndrome [5].

In relation to impact, fatigue has been identified as the consequence of RA that best differentiates between levels of health-related quality of life [6]. Patients have reported the negative effects of fatigue on their well-being, physical activities, emotions, mood, relationships, and social and family roles. From a societal perspective, fatigue is a significant predictor of high health care costs, and is the main reason for work disability and loss [7]. The detrimental effects of fatigue are exacerbated by patients' perceptions that the symptom is a challenge to manage and that it is not routinely addressed in clinical practice. This reluctance to discuss fatigue may reflect the lack of information and available treatments. Consequently, fatigue is widely recognized as important to patients, but how to manage and improve the symptom remains a major unmet need.

A challenge in providing support for RA-related fatigue is that the causes are still unknown. Cross-sectional studies have found that fatigue is associated with pain severity and psychosocial factors including depression, but not disease activity [8]. Overall, the current evidence suggests that fatigue is likely to be caused and maintained by the complex interaction of clinical factors (e.g. inflammation, pain and disability), psychosocial issues (e.g. coping, mood, beliefs and behaviours) and personal factors (e.g. working, caring responsibilities and comorbidities) that may vary both between and within individuals over time [9]. This is reflected in evidence from systematic reviews of non-pharmacological and pharmacological treatments for fatigue, which have identified the potential benefit of physical activity, psychosocial interventions and some biologic DMARDs [10, 11]. The beneficial effect of biologic DMARDs suggests that inflammation has a significant pathobiological role, although fatigue does not completely resolve. Experimental models have found that systemic inflammation leads to increase in intracerebral IFN and TNF-α activity [12]. Furthermore, in collagen-induced arthritis, an animal-model of RA, the blood–brain barrier is porous to cytokines [13]. In patients with RA, a magnetic resonance spectroscopy study suggested that systemic inflammation may affect the neurochemical status of the CNS with high levels of choline to creatine ratio [14].

Possibly due to the lack of clarity around causal pathways, there is an increasing focus on the self-management of fatigue rather than the resolution or cure of the symptom. Recent evidence includes a multicentre randomized control trial using cognitive behavioural approaches. This study found that the impact of fatigue was reduced, with the positive effects maintained at 2 years [15]. Self-management interventions are typically hypothesized to work through the therapeutic mechanisms of enhancing patients' self-efficacy (the belief in their ability to achieve a desired outcome or goal). This is achieved by addressing patients' illness beliefs, their coping strategies and their acceptance of fatigue as a symptom of their RA. In this study, the intervention included the use of daily activity diaries and goal-setting to promote a shift in beliefs and progressive adaptations in how patients cope with fatigue, leading to better knowledge, confidence and reactivation in everyday activities.

Measurement is key to evaluating the usefulness of fatigue interventions, whether the focus is on reducing severity or managing the impact of the symptom. Although OMERACT included fatigue as a core outcome measure in RA, the lack of an RA-specific validated outcome measure led to researchers adopting instruments developed for other conditions to assess fatigue. However, this was resolved in 2013 with the development, testing and publication of the Bristol Rheumatoid Arthritis Fatigue Scale [16]. Designed in collaboration with patients, this multi-dimensional measure captures physical, cognitive, emotional and social aspects of fatigue. In addition, three numerical ratings scales enable researchers and healthcare professionals to measure fatigue severity, impact and coping. As the factors driving and maintaining RA-related fatigue are likely to vary between patients, insight

into how individuals experience and perceive their fatigue could be an important step in providing tailored support.

Patients have identified fatigue as a priority and a challenge to manage. In this supplement, authors have provided updates on the pathobiology, clinical assessment and management of fatigue. Clarifying our current understanding and identifying the gaps in our knowledge is an important step as we continue to look at ways of supporting patients with this common and difficult symptom.

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