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Predictors of fatigue in rheumatoid arthritis

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Abstract

People with RA commonly experience fatigue. Fatigue is a key contributor to increased clinical care costs, primary care consultations and employment loss. Despite this, our understanding of the prognostic of factors of poor fatigue outcomes is lacking and fatigue is poorly managed. Examining longitudinal predictors of fatigue can identify both individuals 'at risk' of poor prognosis, and candidate mechanisms that are worthy of greater inspection. This review discusses the factors most commonly investigated as being implicated in the prognosis of RA fatigue. The available data appears to implicate generic factors such as pain, mental health, disability and sleep as consistent predictors of fatigue outcome, while the role of disease activity and inflammation seems less clear. However, the existing data are not without methodological limitations and there have been no specific studies primarily designed to investigate the inflammatory biomarkers of fatigue. Future studies are required to more comprehensively and robustly determine the mechanisms of fatigue.

Key words: fatigue, inflammation, pain, mood, disability, sleep, rheumatoid arthritis, predictors, mechanisms

Rheumatology key messages

- Fatigue is common in rheumatoid arthritis, yet the symptom is poorly understood and poorly managed.
- Generic factors like pain, mood and disability seem to drive fatigue in rheumatoid arthritis.
- These factors, and therefore optimal fatigue treatment, may be common across chronic diseases.

Introduction

People with RA commonly experience fatigue [1, 2]. Fatigue is the subjective experience of intense tiredness or exhaustion, is often unrelated to energy exertion and not relieved by rest [3]. Prevalence studies consistently report fatigue rates between four and eight times higher (depending on the classification criteria used) [1, 4, 5] than the general population prevalence of 10% [6]. Fatigue may be experienced as a chronic state of weariness or as a recurrent symptom with rapid fluctuations occurring within the same day or between days [1, 2, 7–9]. Regardless, the longer term prognosis is burdensome, with up to 74% of RA patients experiencing persistently high or worsening levels of fatigue [10].

Fatigue has received much attention in recent years, largely in response to work from the OMERACT meetings [11–13], which highlighted the symptom as a core patient outcome. Yet, fatigue remains a key contributor to increased clinical care costs [14], one of the most common reasons for consultation to primary care [15] and a key determinant of sickness absence and loss of employment [2, 7, 15]. Thus, despite this perceived importance and increased research activity, our understanding of the prognostic factors of poor fatigue outcomes is lacking and, subsequently, fatigue is poorly managed.

The longitudinal prediction of fatigue aids the identification of individuals 'at risk' of poor prognosis enabling early targeted intervention. In parallel, such factors are often worthy of greater inspection as candidate mechanisms. To date, evidence regarding the prediction of fatigue is limited. There is a high degree of variation in the type of putative predictors investigated in studies and many factors are investigated in single studies only, making interpretation difficult. For these reasons, this review has focused on discussing the factors most commonly investigated as being implicated in the prognosis of RA fatigue: disease activity and inflammation, pain, sleep, mental health and disability.

Disease activity and inflammation

Historically, fatigue has been perceived to be caused by disease-specific processes, such as inflammation and

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joint damage [16, 17]. Pro-inflammatory cytokines, which are pivotal to RA progression, have been linked to fatigue via sickness behaviour [18] and it is possible that these inflammatory processes initially trigger fatigue in RA [18, 19]. Certainly, while the apparent response of fatigue to inflammation-focused interventions [5, 20–22] would indicate that an association between inflammatory disease activity and fatigue exists, it is now widely recognized that fatigue persists despite receiving the best available care for their disease [23, 24], although anti-inflammatory pharmacological interventions do confer reductions in fatigue in subgroups of patients [20, 25].

Where an association has been observed between inflammation and fatigue prognosis, it has tended to show both that higher [26] and lower [24, 27] inflammation is associated with greater fatigue, depending on the study in question. Further, within a path analysis model [28], we found that when DAS-28 was substituted for ESR or CRP the direct relationship between disease activity and fatigue disappeared, indicating that it may be that the patient reported/influenced (e.g. patient global and tender joints), which drive the associations between DAS-28 and fatigue. Overall, the balance of evidence would seem to indicate that while fatigue prognosis may be associated with composite measures of disease activity [5, 10, 22, 28, 29], it is not consistently predicted by traditional measures of inflammation, such as CRP or ESR [22, 28–30].

Yet, understanding the precise nature of the association between fatigue and inflammatory disease activity is difficult and much of the available data are conflicting and limited. A principal barrier to elucidating the predictive role of inflammatory disease processes in fatigue prognosis is that disease activity can be measured globally, using scales such as the DAS for 28 joints (DAS-28), or by individual components such as measures of inflammation or tender and swollen joints. A second key barrier is that there has been little exploration of fatigue-specific inflammatory biomarkers. Investigations regarding the role of inflammation in fatigue have been limited to studying the prognostic role of the non-specific inflammatory markers typically used in clinic (CRP and ESR). Indeed, evidence from RA and other disease groups that fatigue is predicted by a range of pro-inflammatory cytokines not typically collected in clinics including TNF-α, IL-1, IL-6 and IFN-γ [31–36]. Thus, it may be that there are as yet unidentified specific inflammatory markers of RA-fatigue that, if targeted, could reduce symptom burden.

Pain

Pain is commonly investigated as a possible predictor of fatigue [5, 10, 21, 23, 24, 27, 28, 37–41] and has been identified by patients as a principal cause of their fatigue [7, 42, 43]. Evidence across a number of studies indicates that increased pain is associated both with greater magnitude of fatigue over time [10, 37, 40, 41] and with fatigue persistence [22]. Furthermore, change in pain was not only associated with the magnitude of fatigue change [5, 28], but was also found to mediate the effect of change in disease activity on fatigue outcomes [28]. As a result, some authors have argued that it is pain, not disease activity, that drives fatigue [5, 28], and it has been suggested then that improved pain management should be a key focus of fatigue interventions.

However, van Dartel *et al.* showed that the relationship between pain and fatigue is significant, but synchronous [39], and others have shown that greater fatigue is associated with concurrently higher pain despite disease remission [23, 24]. Thus, while it is clear that the two symptoms are associated, the link between the symptoms may be due to the existence of a shared aetiology, such as central sensitization [44, 45] rather than 'cause and effect' *per se*. Irrespective of this, it seems likely that interventions seeking to reduce pain may have beneficial effects on fatigue.

Sleep

Proposing the existence of a relationship between sleep and fatigue would appear intuitive, because it is clear that disturbed sleep leads to tiredness and daytime sleepiness. However, while overlapping in description, sleepiness and tiredness are distinct from fatigue [7] and the nature of their association is unclear. Furthermore, sleep is a complex behaviour that is composed of both subjective and objective components and, despite the rise in availability of sleep and activity trackers [46], few studies have measured both components [47]. Nevertheless, studies have indicated that there is an association between the magnitude of sleep problems reported and corresponding levels of fatigue [40, 48, 49] and that baseline levels of sleep problems were higher among individuals who did not go on to experience improvements in fatigue [10]. On the other hand, others have shown that the relationship between sleep problems, or use of sleep medications, and fatigue is not significant [22, 27, 38].

The most convincing evidence regarding the relationship between sleep and fatigue arises from the experimental literature, which show that experimentally induced sleep deprivation has been associated with increased fatigue [50, 51]. It is important to consider though that there appears to be a complex interplay between sleep, pain and fatigue [50–52]. None of the available studies were found to determine whether disturbed sleep has a direct effect on fatigue, or whether its effect might be indirect and mediated through the elevated pain levels that are observed following episodes of poor sleep [52, 53]. It is clear that further work is needed to determine the precise temporal nature and pathways between both objective and subjectively recorded sleep and resultant changes in fatigue.

Mental health

The relationship between mental health and fatigue appears to be particularly important, as poor mental health both predisposes an individual to, and perpetuates, fatigue [54–56]. Mental health may typically be defined in many ways, such as previous diagnosis of depression [10, 21, 28, 54–56], current levels of dysphoria [54–56] or

position on a mental health continuum (e.g. Short Form 36 Mental Health Scale) [10, 21, 22, 28, 57], or use of antidepressants [10, 21]. Irrespective of the definition, the evidence indicates that higher depression scores, or ratings of dysphoria, in combination with previous history of depression is associated with an exacerbation of, or failure to improve, fatigue [10, 21, 29, 54–57]. Evidence also indicates that less improvement in mental health complaints is associated with less concurrent improvement in fatigue [28, 29, 56], and that mental health remains poor among those who experience persistent fatigue despite disease management [22, 23]. However, it is important to acknowledge that fatigue is included as a symptom in diagnostic criteria for depression [58], so delineating the predictive nature of the relationship can be complicated.

Far fewer studies have investigated the link between fatigue and other aspects of mental health such as anxiety and stress, but evidence would seem to indicate that anxiety, stress and negative interpersonal events are associated with poor fatigue prognosis [36–38, 59].

Disability

Levels of disability, largely measured by the Stanford HAQ, have consistently linked high levels of disability to reduced likelihood of improvement, greater likelihood of persistence [10, 21–23, 29, 60], and a greater magnitude of fatigue over time [38, 40]. It is clear that the swelling and progressive joint damage that characterize RA may increase the magnitude of effort required to complete daily tasks and lead to increased fatigue. In the era of biologics and bio-similars, interpreting the role of disability in fatigue is complicated, as many of the patients more recently diagnosed will avoid the year-on-year progression of joint damage and disability that once typified the course of RA [61, 62], but continue to report fatigue. That being said, fatigue has been referred to as a disabling symptom [42, 43], and one that makes completion of daily tasks difficult, if not impossible. Given the non-specific nature of disability questionnaires such as the HAQ (e.g. 'Are you able to wash and dry your entire body?') it is not clear the extent to which fatigue at the time of reporting has influenced the levels of disability recorded for participants.

Limitations of the available data

It is first worth highlighting that a range of measures exist to study fatigue within RA populations [9, 63]. These measures, which have been validated to a greater or lesser extent within the population, may measure various things such as the magnitude or qualities of fatigue, including severity, impact or coping (e.g. Bristol Rheumatoid Arthritis Fatigue Scale Multidimensional Questionnaire (BRAF MDQ), or Numerical Rating Scales (BRAF NRS)). Measures may also distinguish between mental and physical fatigue (e.g. Chalder Fatigue Scale) or include assessment of both the quality and type of fatigue, such as measuring physical fatigue, emotional fatigue and the social consequences of fatigue (e.g. Functional Assessment Chronic Illness Therapy (Fatigue)). Finally, measures may position people on a continuum from energy to fatigue (Short-Form 36 Vitality (SF36 VT)). It is clear that the measures used may have substantial impacts on the associations observed if a predictor is differentially associated with distinct dimensions of fatigue [9]. It is notable that few studies have used scales that capture the multidimensionality of fatigue, instead relying on single-item visual analogue scales, or numerical rating scales [5, 10, 24, 26, 27, 29, 30, 37, 41, 49, 54, 56, 57]. Equally, there is no consistency in the definitions and measures used to capture exposures of interest and no single study has investigated all predictors of interest, making it likely that residual confounding exists and precluding the development of an evidence-based causal model/diagram of fatigue.

In addition, many of the longitudinal studies available are methodologically compromised, being limited to infrequent (i.e. yearly), or short-term (i.e. one week) fatigue assessments, in small samples. As a result, many studies have predicted fatigue over disparate time points or have tended to aggregate longitudinal data to investigate the 'normal' pattern of fatigue, despite high within- and between-person variation. Such analyses are particularly problematic, given growing evidence regarding the likely existence of fatigue sub-types [10, 64–66]. Therefore, while the available evidence can provide some interesting insights into the possible predictors of fatigue, it is clear that additional, more methodologically robust, studies are needed.

Are the causes of RA-fatigue disease specific?

On balance, and based on the available evidence, it appears likely that the predictors of fatigue are not unique to RA populations. Rather, some of the most consistent candidates have been identified as predictors in other rheumatic diseases, such as osteoarthritis and fibromyalgia, as well as in a broader range of long-term medical conditions such as multiple sclerosis and cancer [2, 5, 18, 19, 28, 48, 50, 51, 54, 55, 67–71]. Together, this points towards an as yet untested hypothesis that fatigue, its prognostic factors, and therefore its optimal treatment strategy, may be common across many long-term illnesses, irrespective of whether they have an inflammatory aetiology. Future studies may benefit from investigating this hypothesis with a view to developing generic fatigue interventions across a range of chronic conditions.

Conclusion

People with RA commonly experience fatigue. Despite the perceived importance of, and increased research activity regarding, fatigue, the symptom's prognosis remains poorly understood and poorly managed. The available data appears to implicate generic factors such as pain, mental health, disability and sleep as consistent predictors of fatigue outcome, while the role of disease-specific factors such as inflammatory processes seems less clear. However, there have been no specific studies conducted to investigate the inflammatory biomarkers of fatigue and available studies are limited to those with

infrequent and short follow-up, or examinations of average prognosis over time. Thus, while insightful, the existing evidence is not definitive and future studies are required to more comprehensively and robustly determine the mechanisms of symptom prognosis over time.

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