Correlations between fatigue and disease duration, disease activity, and pain in patients with rheumatoid arthritis: a systematic review

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Objectives: Rheumatoid arthritis (RA) patients suffer from disabling fatigue but the causes of this condition are unknown. Our aim was to assess which of the variables disease activity, disease duration, and pain is associated with fatigue.

Method: We conducted a systematic literature search in MEDLINE and EMBASE, followed by selection of studies according to set criteria, data extraction, and statistical analyses of the relationships in RA between fatigue and the following covariates: disease duration, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), the 28-joint Disease Activity Score (DAS28), swollen to tender joint count ratio (STR), and pain. Linear regression analyses of fatigue regressed on each of the six covariates, and a multiple regression analysis where fatigue was regressed on the six covariates through a forward selection procedure was carried out with construction of correlation measures between fatigue and the covariates.

Results: A total of 121 studies were included in the analyses, including > 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 the STR or disease duration, with pain as the overall dominating factor.

Conclusions: Fatigue has a substantial influence on the lives of RA patients, independent of disease duration. Pain is the dominating factor in the experience and degree of fatigue. Disease activity is positively correlated to fatigue but does not contribute substantially when pain is considered. Optimal pain relief is therefore an important part of the treatment to improve fatigue in RA.

Rheumatoid arthritis (RA) is a chronic autoimmune joint disease with synovial inflammation, joint pain, joint swelling, and erosion (1). It has been estimated that the prevalence of RA in adults in the USA and Europe is 0.4–1.0% (2), and in the UK the disease affects 0.81% of the adult population, with the female/male ratio being almost 3:1 (3), while the prevalence in Norway is 0.44% (4), and a lower prevalence is reported in Southern Europe and in developing countries (2).

Apart from pain and disability, RA patients suffer from fatigue (5). Fatigue is a subjective feeling of complete exhaustion that does not seem to decrease, even after rest (6). The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have identified fatigue as an outcome of great importance to patients, and have recommended that fatigue should be reported in every trial with RA patients (7).

Patients describe their fatigue as physical or mental fatigue, very often occurring together (6). Fatigue can be very disabling. The patients feel tired, depressive, frustrated, and unable to complete their daily tasks (5, 8).

The aetiology of fatigue is still unknown. This of course makes it a greater challenge to treat. Fatigue is potentially secondary to other disease variables, and it would therefore be of great importance to identify these disease characteristics.

Previously, the first drug of choice in the treatment of RA was a disease-modifying anti-rheumatic drug (DMARD), especially methotrexate (9). Within the past few years, biological therapy including tumour necrosis factor (TNF)-α inhibitors has proven to reduce the inflammation and some of the symptoms effectively. The biologics are given either in combination with...
methotrexate or as monotherapy (10, 11). Biological therapy, along with an attempt to start treatment as early as possible, is a step towards the appearance of a less aggressive disease, and it has slowed down the progression of the disease. However, in some studies biologics have not been shown to have a substantial effect on the fatigue experienced by the patients, despite an improvement in disease activity (12), while other studies do find a positive effect of treatment on fatigue with biologics (13, 14). In recent studies fatigue was not found to be clearly related to disease activity (15, 16). With the lack of clarity of the underlying causes of fatigue and the difference in patient populations in studies looking at fatigue, it is of interest for the clinician to know what will be the strongest factors influencing the experience of fatigue.

We have therefore chosen to look at the most likely factors influencing fatigue in RA, that is disease duration, disease activity, and pain. Based on the present knowledge of fatigue in RA, we addressed the following hypotheses: in patients with RA (1) disease duration is positively correlated to fatigue; (2) disease activity is positively correlated to fatigue; and (3) pain is positively correlated to fatigue.

The overall aim of this systematic literature review was to assess whether, in RA, there is a positive association between fatigue and one or more of the disease variables: disease duration, disease activity, and pain.

Method

The protocol for this study was registered in PROSPERO (www.crd.york.ac.uk/PROSPERO): CRD 42013004178, prior to study start.

Literature searches

The bibliographic databases MEDLINE using PubMed from 1966 and EMBASE using Ovid from 1974 were searched, both up to March 2014. The following search strategy was applied ‘Rheumatoid in Ti AND fatigue’ with limitations: Human(s).

Criteria for considering studies in this review

Only studies available in English were included. Case studies were excluded.

Participants. Patients aged ≥18 years diagnosed with RA according to the American College of Rheumatology (ACR) criteria or similar were included (7, 17, 18). Otherwise no exclusion criteria concerning the patient group were applied.

Outcome measures. The primary outcome was fatigue. All included studies must therefore contain measures of fatigue. If a study reported more than one fatigue measure, we chose one according to the following order:

- Multidimensional Assessment of Fatigue (MAF)
- Fatigue Symptom Inventory (FSI)
- Checklist Individual Strength (CIS)
- CIS, severity subscale
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)
- Medical Outcome Study (MOS) 36-item Short Form Health Survey [SF-36 (Vitality)]
- Visual Analogue Scale (VAS)
- Fatigue Assessment Scale (FAS)
- Numeric Rating Scale (NRS)
- Five-point scale

Included studies should also report one or more of the three outcomes:

1. Disease duration
2. Disease activity, measured as:
   - Disease Activity Score (DAS28) (19)
   - C-reactive protein (CRP)
   - Erythrocyte sedimentation rate (ESR)
   - Swollen to tender joint count ratio (STR: assuming that this ratio ≥1 indicates inflammation) (20)
3. Pain, on a VAS or NRS (21)

Selection of studies

Titles and abstracts of the identified studies were evaluated by SGM and EMB. Studies that clearly did not fulfill the inclusion criteria according to the title and abstract were excluded. If only one of the reviewers judged a study to be included, it was included at this stage. The studies selected for inclusion were viewed in full text by SGM and EMB for further selection, and studies found not to fulfill the inclusion criteria in this group were also excluded. If any questions about inclusion/exclusion occurred, BDS moderated such that if two authors voted for inclusion, the study was included.

Data extraction and data handling

Data from the included studies were extracted by SGM. These were measures of fatigue and the covariates disease duration, disease activity, and pain. Measures of fatigue were all given as numerical scales that had to be normalized for direct comparison. This is a technique also used when carrying out meta-analyses for Cochrane Reviews in RevMan (22). We normalized into a scale from 0.0 to 1.0 (0.0 = no fatigue and 1.0 = worst possible fatigue). Pain was normalized in a similar way.

Statistics

The relationships between fatigue in the form described in the section on outcome measures and the covariates...
disease duration, ESR, CRP, DAS28, STR, and pain were investigated. Linear regression analyses of fatigue, regressed on each of the six covariates, were performed based on the selected studies, and a multiple regression analysis, where fatigue was regressed on the six covariates through a forward selection procedure, was carried out.

Correlation measures between fatigue and the covariates were constructed; first, in the form of correlation between the individual measures of fatigue and the six covariates in the studies, treating these measures as descriptive meta-data, and applying standard correlation estimates to these data. Second, the correlation was estimated from the same meta-data but using weights for the estimation, where the sizes of the individual included studies were used as inverse weights. All 12 correlation measures were afterwards simulated 50 000 times, using Gaussian variables for each repetition, and constructing the similar correlation measure under the assumption of no true correlation. The simulations were used to determine a p-value for each correlation measure, under the hypothesis of no correlation.

As missing data excluded the possibility of a standard multiple regression analysis, fatigue as a function of pain was modelled with a standard regression. This model was then extended by adding one of the other covariates at the time (a forward selection procedure based on the Akaike information criteria (24) divided by the number of data studies without missing information for all statistically significant extensions), and then removing any statistically insignificant terms before including the next.

Fatigue measures were plotted against each of the six covariates individually to obtain a graphical presentation of the correlations.

Results

The literature searches resulted in 1041 references after removal of duplicates. Of these studies, 686 did not fulfil the inclusion criteria and could be excluded at title/abstract level. A total of 355 studies were viewed in full text. Of these, 121 studies, including a total of 102165 RA patients, were included for systematic review and analysis in this study. Many of the included studies had more than one study arm, resulting in 184 data sets. Four studies (six data sets) represent more than half the total number of RA patients in this study and, because of this heterogeneity, the correlation analysis was carried out with both plain and weighted calculations. The study selection process is shown in Figure 1. Characteristics of the 121 included studies are shown in online Appendix 1.

Outcome measures

A wide range of scales was used to assess fatigue. VAS was the most frequently used and was applied in 69 of the 121 studies. In all, 15 different scales were applied in the 121 studies. All data on fatigue were normalized into a common scale from 0 to 1. The minimum and maximum values of fatigue found in the data from the 121 included studies were 0.13 and 0.81, respectively, with a mean for all studies of 0.5 (range of scale 0–1).

All studies had considered at least one of the covariates, but only one of the 121 studies included data on all six covariates considered (disease duration, DAS28, ESR, CRP, STR, and pain). Pain and disease duration are the variables reported in most studies: 103 and 72, respectively. CRP was the least reported outcome, followed by DAS28 and ESR (Table 1). A graphical presentation of fatigue as a function of each of the variables is given in online Appendix 2. A table of correlation measures between fatigue and covariates with p-values for statistical significances is given in online Appendix 3.

Table 1. Number of studies (out of 121) that each of the disease variables (pain, ESR, CRP, DAS28, joint counts, and disease duration) apply to, along with the number of RA patients included in these studies.

| Variable          | No. of studies | No. of patients |
|-------------------|----------------|-----------------|
| Pain              | 103            | 98241           |
| ESR               | 33             | 15476           |
| CRP               | 22             | 14450           |
| DAS28             | 34             | 14906           |
| STR               | 40             | 27102           |
| Disease duration  | 72             | 69552           |

ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; RA, rheumatoid arthritis; STR, swollen to tender joint count ratio.

Retrieved from search in MEDLINE and EMBASE following duplicate removal 1041 records

Reviews or studies excluded based on title and abstract 686

Viewed in full-text 355

Not fulfilling inclusion criteria 234

Included studies 121

Figure 1. Flow diagram showing the selection process of the studies.
In the included studies, disease duration was given as a mean of a relatively large group, and the standard deviation (sd) and ranges were often substantial. There were 72 studies with data on disease duration. Where only one common value for disease duration was given for all study arms, the disease duration was not included in the analyses. However, a study would only be excluded from the current review if there were none of the other of the chosen covariates reported relating to patients in a particular study arm. The mean disease duration of all studies was 10.4 years. Mean values ranged from 0.23 to 21 years.

Apart from analysing the direct correlation between fatigue and disease duration, we chose to look at ‘recent onset RA’ (< 3 years) vs. ‘established RA’ (> 3 years) to determine whether there was a difference in level of fatigue between the ‘recent onset’ and the ‘established’ group (online see Appendix 2). In no circumstances did disease duration show any correlation with fatigue (p > 0.5).

CRP and ESR. As CRP has recently become a more standard biochemical parameter for disease activity in the clinic, CRP was mainly presented in the more recent studies, while ESR was mainly presented in the older studies (online see Appendix 1).

Fatigue was significantly positively correlated to CRP (p = 0.0002 when the studies were not weighted according to the number of included patients, and p = 0.006 when weighted according to the number of included patients), with a high CRP indicating more fatigue.

ESR was significantly positively correlated to fatigue, if we did not weight the data according to the number of patients in each study (p = 0.0009). When weighted with the number of patients in each study, the correlation was statistically insignificant (p = 0.09).

DAS28. Of the included studies, five used DAS28 (CRP) and 29 used DAS28(ESR). Ten studies did not report using either CRP or ESR in their DAS28. These studies were not included in our analyses. Wells et al (24) and Nielung et al (26) have shown that there is good agreement between DAS28(CRP) and DAS28 (ESR). We therefore decided to pool all data with DAS28(CRP) or DAS28(ESR).

Fatigue was significantly positively correlated to DAS28(CRP) or DAS28(ESR), with p = 0.0001 when not weighted according to the number of included patients, and p = 0.04 when weighted according to the number of included patients; that is, a high DAS28 indicating more fatigue.

Swollen joints/tender joints. The STR did not correlate to fatigue (p > 0.4).

Pain. Pain was mainly measured as variations of VAS or NRS, and only eight studies used other scales, such as SF-36-Pain, Health Assessment Questionnaire (HAQ)-Pain, arthritis pain [Arthritis Impact Measurement Scales 2 (AIMS2), McGill-Pain, and the Nottingham Health Profile (NHP)-Pain (26–30). Data on pain were normalized to a scale of 0–10.

Fatigue was significantly correlated to pain (p < 0.0001), both when weighted for the number of patients in each study and with no weighting. The coefficient of the correlation is positive, that is the more pain the more fatigue (online see Appendix 2).

Multiple regression analysis

Because of the inadequate number of studies reporting data on three or more variables, setting up a general multiple regressions model for fatigue was not possible. The multiple regression model created instead, adding one covariate at a time to the model of fatigue as a function of pain, showed, after inclusion of all remaining covariates, that the only resulting significant covariate was pain, that is pain is the dominating factor in the experience and degree of fatigue. When considered simultaneously with pain, the covariates DAS28, CRP, and ESR thus do not add significantly to the modelling of fatigue, despite these covariates correlating significantly to fatigue when considered on their own. The information they give on fatigue is therefore essentially contained in the covariate pain. The result did not depend on the fact that pain was chosen as the initial covariate in the model for fatigue.

Discussion

The aim of this study was to analyse the correlates of fatigue with six different disease variables. Our results show that fatigue is positively correlated with pain, CRP, DAS28, and ESR but not with the STR or disease duration. In general, it is important that the meta-data and the weighted data were almost the same, except for ESR.

From the multiple regression analysis, where all covariates were considered simultaneously, pain was found to be the overall dominating factor. The additional information contained in the other covariates was negligible when the covariates were considered simultaneously with pain.

Impact of fatigue in the RA population

When looking at all data on fatigue, a high level of fatigue is seen. A mean of 0.5 (range of rating scale: 0–1) is very high, especially as this is based on more than 100 000 RA patients. Considering that many of these RA patients were well-treated, fatigue is a very real problem for this patient group, and emphasizes that fatigue has a large impact on the lives of RA patients (5, 7).

Fatigue is measured widely, even in studies not looking at fatigue. This clearly indicates that health
professionals dealing with RA patients are aware of the fact that fatigue is a major problem in this patient group. Unfortunately, there has so far not been a reliable treatment to reduce fatigue.

Disease duration and fatigue

Disease duration was found not to influence fatigue. This is somewhat unexpected. We would have predicted that longer disease duration, leading to erosions, and living with affected joints for many years would lead to a higher degree of fatigue. On the contrary, our findings show that RA patients experience high levels of fatigue in both the early and the later stages of their disease. The reason why disease duration does not correlate with fatigue could be due to too little variation in disease duration, but when looking at our data (online Appendix 2), this is not the case. Disease duration in the 121 included studies was evenly distributed between 0 and 21 years.

Disease activity and fatigue

Disease activity can be measured as inflammation with the non-specific biomarkers for inflammation ESR or CRP or with more complex scores such as the composite measure DAS28 (24, 25), including a factor for inflammation based on either ESR or CRP.

Even though ESR was not significantly positively correlated to fatigue when weighted according to the number of patients in the studies, there is a clear tendency towards a positive correlation (online see Appendix 2). For CRP, there was a positive correlation with fatigue when applying both methods of data handling. Inflammation does therefore correlate to fatigue.

DAS28 is currently one of the most applied assessment tools for disease activity in RA. It uses several dimensions of the disease to evaluate disease activity, with number of swollen and tender joints, measures of general health, and the acute-phase response (ESR or CRP). DAS28 was found to be positively correlated to fatigue but not as significantly as pain and CRP. DAS28 has several components, and this may blunt this measure compared to a direct measure of inflammation, as the weighting of the various components of DAS28 is different, and some components may be more inflammation related than others.

We included the STR under the assumption that this is an indicator of inflammation (20). We found that this ratio does not correlate with fatigue. This may simply be because this composite measure is not sensitive enough to show a correlation with fatigue.

Pain and fatigue

Pain was found to be the overall domineering factor behind the condition fatigue in RA. Disease activity is correlated to fatigue but pain is the main factor. This is in accordance with findings by Druce et al (16), and it also supports the idea that pain hypersensitization may play a role in part of the RA population (31). To diminish fatigue, treatment of inflammation will of course have some impact, but our analysis shows that the treatment impact will be through the reduction in pain. An efficient pain treatment from the time of diagnosis should probably be added to all other treatments.

Limitations of study

Our search revealed a large number of studies. However, the general lack of studies reporting data on several disease variables and not only on pain was a drawback and could be a source of bias. It also made a general multiple regression analysis approach impossible. A general multiple regression model would have made our study statistically stronger, but differences in the number of reported outcome parameters between studies gave missing data for some of the parameters, making it impossible to use a general multiple regression model. The missing data were, however, clearly missing ‘at random’. In particular, we could have investigated in more detail the degree to which the combined information on DAS28, CRP, and ESR could explain the impact of pain on fatigue.

With the correlation model applied here, we can only draw conclusions on the degree of correlation between fatigue and the described covariates.

Pain is reported in about three times as many studies as the remaining variables (Table 1). When considering the total number of patients assessed within the different groups of variables, there is an even greater ratio between the amount of reported pain and the amount of other reported variables. However, the number of studies and the total number of patients where a particular variable is recorded are still substantial, with more than 14000 patients in the group with the lowest number of patients assessed for this variable (CRP).

It was not possible with the obtainable data to relate fatigue to categories of disease activity. This may have influenced the findings to some degree, but although pain is the main factor affecting the fatigue condition, our data show that higher disease activity gives a higher degree of fatigue.

We chose to show both weighted (according to the number of patients in a study) and unweighted data (each study arm representing one data point). The problem with the weighted approach is that it may be oversensitive to the effect of large studies, and therefore not give an appropriate summary measure for the correlation, thereby in practice excluding the results from the majority of the included studies. With the unweighted approach there will always be a question of very small patient groups, which may alter the results in a direction
that the power of the smaller studies cannot support. The problem concerning weighted or unweighted data is, however, small in our present study, as our data in general show the same results when applying both weighted and unweighted methods. We therefore have confidence in the presented findings.

Conclusions
Fatigue has a substantial influence on the lives of RA patients, independent of disease duration. Pain is the domineering factor in the experience and degree of fatigue. Disease activity, measured as DAS28, CRP, or ESR, is also positively correlated to fatigue but does not contribute to a high degree when pain is considered. Based on our findings, pain must be considered an important factor when designing treatment for RA patients with the intention to improve fatigue in these patients.

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Supporting information
Additional Supporting Information may be found in the online version of this article.

Appendix 1. Description of the 121 included studies, giving extracted data.
Appendix 2. Graphic representation of the correlations between fatigue and the covariates.
Appendix 3. Table showing p-values for correlations between fatigue and the covariates un-weighted (plain) and weight.

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