Study Protocol

Rheumatoid Arthritis and Fatigue

Correlations between fatigue and disease duration, disease activity and pain in patients with rheumatoid arthritis – A systematic literature review

Simone Groth Madsen[1], Bente Danneskiod-Samsøe[1], Else Marie Bartels[1]

[1]The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark

Contact person:

Else Marie Bartels, PhD, Dsc

The Parker Institute

Copenhagen University Hospital, Bispebjerg and Frederiksberg

Nordre Fasanvej 57

Dk-2000 Copenhagen F

Denmark

Tel: +45 38164168

Email: else.marie.bartels@regionh.dk

Introduction

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 western countries (USA and northern Europe) is 0,4-1,0 % (2). In England the disease affects 0,81% of the adult population, with women:men-ratio being almost 3:1 (3), and in Norway the prevalence is 0.44 %(4). The prevalence is lower in Southern-European countries and in developing countries(2).

Apart from pain and disability, many RA patients suffer from fatigue(5). Fatigue is a subjective feeling of complete exhaustion that does not seem to fade away even after rest (6). The ACR and EULAR have identified fatigue as an outcome of great importance to patients and they have recommended that fatigue should be reported in every trial with RA patients (7).
The patients describe their fatigue to be physical or mental fatigue, very often occurring together (6). Fatigue can be very disabling; the patients feel tired, depressive, frustrated and are 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. It would be of great interest to identify these disease characteristics

Previously, first drug of choice in the treatment of RA was Disease-modifying-antirheumatic drugs(DMARDs), especially Methotrexate (9). Within the last couple of years, biologic therapy such as 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 mono-therapy (10;11). Biologic therapy, and an effort to start treatment as early as possible, is a step towards appearance of a less aggressive disease and it has slowed down the progression of the disease. But the biologics has though not seemed to have a substantial effect on the fatigue experienced by the patients (12).

Based on the present knowledge of fatigue in RA, we will address the hypotheses:

1) In patients with RA, disease duration is positively correlated to fatigue
2) In patients with RA, disease activity is positively correlated to fatigue
3) In patients with RA, pain is positively correlated to fatigue

Aim/Objectives

The aim of this systematic literature review is to asses whether there is a positive association between fatigue and one or more of the disease variables; disease duration, disease activity, and pain.

Methods

Literature searches

The following bibliographic databases will be searched:
MEDLINE via PubMed from 1966 to present, and EMBASE via Ovid from 1974 to present

Search strategy:

Rheumatoid in Ti AND fatigue. Limitations: Human(s)

Criteria for considering studies in this review

Only studies available in English will be included.
The study must include a cohort, and case studies are excluded.

Participants

We will include studies with patients aged ≥ 18 years diagnosed with RA according to the ACR criteria or similar (13-15). Otherwise no patient selection will occur.

Outcome measures

The primary outcome is fatigue. All of the included studies must therefore contain measures of fatigue. If a study reports more than one fatigue measure we will choose one according to the following order:

- **MAF**, Multi-dimensional Assessment of Fatigue
- **FSI**, Fatigue Symptom Inventory
- **CIS**, Checklist Individual Strength
- **CIS, severity subscale**
- **FACIT-F,** Functional Assessment of Chronic Illness Therapy- Fatigue
- **MOS SF-36 (Vitality)**, Medical Outcome Study – Short Form health questionnaire
- **VAS**, Visual Analogue Scale
- **FAS**, Fatigue Assessment Scale
- **NRS**, Numeric rating scale.
- **5-point scale**

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

a)Disease duration.

b)Disease activity, measured as Disease Activity Score (DAS(28)), C-reactive Protein(CRP), Erythrocyte Sedimentation Rate(ESR), or number of swollen and tender joints.

c) Pain, on a Visual Analogue Scale (VAS)

Selection of studies

The title and abstract of the identified studies will be evaluated by SGM. If in doubt EMB will be consulted. Studies that clearly do not fulfil the inclusion criteria according to the title and abstract will be excluded. The remaining studies will be viewed in full text by SGM and EMB for further selection, and studies found not to fulfil the inclusion criteria in this group will also be excluded. If any questions about inclusion/exclusion occur BDS will moderate

Data extraction and data handling

Data from the included studies will be extracted by SGM. Measures of fatigue, disease duration, disease activity and pain will be presented in a table.

If measures of fatigue are not comparable, they will be normalized into a scale from 0,0 - 1,0 (0,0= no fatigue and 1,0= worst possible fatigue).

Pain will be normalized in a similar way, if necessary.

Linear regression and Pearson's R-value will be calculated to see whether fatigue is positively correlated to either of the disease variables.
Fatigue measures will be plotted against disease duration, disease activity and pain. Since disease activity can be measured in several different ways fatigue will be plotted against each of the identified measuring methods individually.

Results

Fig. 1:
Flow diagram of the selection process of studies.

Table 1:
Description of included studies with outcomes

Fig. 2 ->
Fatigue as a function of disease duration, disease activity and pain.

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