Fatigue in knee and hip osteoarthritis: the role of pain and physical function

Gijs F. Snijders¹, Cornelia H. M. van den Ende¹, Jaap Fransen², Piet L. C. M. van Riel², Mirelle J. P. M. Stukstette¹, Koen C. Defoort³, Marianne A. Arts-Sanders¹, Frank H. J. van den Hoogen¹ and Alfons A. den Broeder¹ on behalf of the Nijmegen OsteoArthritis Collaboration (NOAC) study group

Abstract

Objectives. It is suggested that serious levels of fatigue are present in nearly half of patients with OA. However, it is unclear which dimensions of fatigue are involved, if fatigue is related to pain and physical function, and if fatigue is influenced by therapy. The aims of this study were to measure levels of different dimensions of fatigue before and after evidenced-based conservative treatment and to investigate the association between fatigue and pain and physical function in patients with knee or hip OA.

Methods. In this observational cohort study, levels of different dimensions of fatigue were measured in knee and/or hip OA patients before and after 12 weeks of conservative treatment. Cross-sectional and longitudinal relations between (change in) fatigue dimensions and (change in) pain or physical function were studied using association models, controlling for predefined possible confounders.

Results. A total of 231 patients was included, with 47% experiencing severe fatigue. A small decrease in levels of fatigue was seen after standardized treatment. The level of fatigue severity was cross-sectionally- and longitudinally associated with physical function, whereas the level of physical fatigue was cross-sectionally and longitudinally associated with pain and physical function. No confounders were identified.

Conclusions. Important levels of fatigue are common in knee and hip OA patients. After evidence-based tailored conservative treatment targeted to improve pain and physical function, a small decrease in fatigue levels was found. Reduction in levels of different fatigue dimensions were related to the change in physical function and pain.

Key words: Knee osteoarthritis, Hip osteoarthritis, Fatigue, Standardized conservative treatment, Pain, Physical function, Treatment guidelines.

Introduction

In patients with chronic diseases, fatigue is often rated as one of the key factors leading to a decreased quality of life [1]. Regarding OA, a focus group study indicated that OA patients experience notable amounts of fatigue that has a substantial impact on their lives [2]. The few studies on fatigue in OA report marked levels of fatigue in nearly half of patients [3-6]. These findings are comparable with levels found in RA [4].

Cross-sectional and some longitudinal data show that a large amount of variability exists in (the course of) fatigue in OA patients [4, 5]. Therefore, identifying variables associated with (change in) fatigue could be valuable. Gaining more insight into these factors could lead to more insight into the pathophysiology of fatigue in OA. Moreover, modifying these factors may lead to a reduction of fatigue experienced by OA patients. Up to now, several factors...
associated with fatigue in OA have been identified, such as older age, more pain, less physical activity, lower positive affect, depression and lower CRP in serum [4, 5, 7]. Of these factors, especially the influence of mental health (depression in particular) and other psychosocial factors on fatigue seems to be substantial [5, 6]. What is more, depression may be a factor on the causal pathway between physical function and fatigue [8].

Studies concerning fatigue in OA published thus far have some limitations. First, included subjects were inadequately characterized, without use of widely accepted classification criteria [9, 10]. Second, no distinction between different dimensions of fatigue—like, for example, subjective fatigue, concentration, motivation and physical activity—was made. It could be hypothesized that increased levels of fatigue solely exist in particular dimensions and that each dimension has different determinants. Lastly, the aforementioned studies were mostly cross-sectional and non-interventional, thus limiting the possibility to draw conclusions about the direction of causality.

Fatigue severity in OA seems to be related with clinical and psychological factors; however, the precise causal pathway remains unclear. It could be conceived that increased fatigue in OA is mainly caused by increased pain and/or decreased physical function. This is supported by studies targeting fatigue in RA [11, 12]. Improvement in pain and daily functioning as recommended in treatment guidelines for knee and hip OA [13–17] should—following this line of reasoning—lead to lower levels of fatigue, but this has not been studied yet.

The aims of this study were therefore (i) to investigate levels of different dimensions of fatigue in knee and hip OA; (ii) to assess changes in fatigue after evidence-based tailored conservative treatment targeting pain reduction and physical functioning; and (iii) to study the cross-sectional and longitudinal relations between (change in) fatigue with (change in) pain and physical function in patients with knee or hip OA.

Patients and methods

Design

Levels of different dimensions of fatigue were measured in an observational cohort study before and after evidence-based tailored multimodal conservative treatment in knee and hip OA patients. Subsequently the cross-sectional and longitudinal relation (after 12 weeks of standardized treatment) between the fatigue dimensions and the supposed determinants of pain and physical function were studied. The local Medical Research Ethics Committee (MREC) of the Arnhem-Nijmegen (The Netherlands) region approved the Cohort of Non-invasively Treated Osteoarthritis of Lower extremities-Pain, Function and Radiological Outcome (CONTROL-PRO) study (local study number 2009/095). Moreover, all procedures followed were in accordance with the Helsinki Declaration. All participants gave their written informed consent.

Patients

All patients referred to the specialized knee and hip OA outpatient clinic (knie en heup arthose poli) at the Department of Rheumatology of the Sint Maartenskliniek and participating in the CONTROL-PRO study were considered for inclusion in this study. The main objective of the CONTROL-PRO study is to investigate the disease course of patients with moderately advanced (secondary care) knee and hip OA receiving standardized non-invasive multimodal treatment.

For participation in CONTROL-PRO, patients had to fulfil the clinical ACR criteria for knee and/or hip OA [9, 10]. For knee OA, the following criteria were used: knee pain (>15 days of last month) plus at least three of the following: age >50 years, morning stiffness <30 min, crepitus, bony tenderness, bony enlargement and no palpable warmth. For hip OA, the following criteria were used: hip pain (>15 days of last month) plus internal rotation of the hip <15° and ESR <45 mm/h or hip pain (>15 days of last month) plus internal rotation of the hip ≥15° and painful internal rotation of the hip and morning stiffness ≤60 min and age >50 years.

Exclusion criteria were inflammatory rheumatic diseases or deposition diseases possibly leading to inflammatory arthritis or secondary OA, comorbidity exceeding the complaints of limitations of knee or hip OA, cognitive or sensorimotor problems interfering with the use of questionnaires and planned orthopaedic procedures within the next 12 weeks. Allowed were calcium pyrophosphate deposition disease (CPDD) (excluding the phenotypes pseudogout and polyarthritis) and previous meniscus problems.

Standardized conservative treatment

Patients who were treated at the knee and hip OA outpatient clinic received standardized evidence-based tailored conservative treatment in a stepped-care format as usual care for 12 weeks if they experienced knee and/or hip pain on a numeric rating scale (NRS, 0–10) >4. The stepped-care model was based on a Dutch multidisciplinary guideline (published online) for diagnosis and treatment of knee and hip OA and has been proposed by a consensus panel of leading experts in the field of OA in The Netherlands [18, 19].

The goal of the intervention was to reduce the level of pain on the NRS to <4. The study visits were planned at Weeks 0 and 12 at the outpatient clinic and at Weeks 4 and 8 by telephone and managed by a research physician (G.F.S.), a physician assistant or a nurse practitioner (M.A.A.-S.). When NRS pain remained >4 and patients had adequately taken the prescribed medication for at least 2 weeks, treatment options outlined in the next step of the stepped-care model were offered.

The first step of the treatment protocol consisted of education, lifestyle advice concerning physical activity and weight loss in patients with a BMI of ≥28 (goal 5% weight loss in 12 weeks), referral for physical therapy (prescription for both aerobic and strengthening exercises
according to the graded activity principle [20], and treatment with paracetamol (acetaminophen) in a fixed dose of 1000 mg three times a day (in case of no recent use for knee and/or hip complaints). In the second step, if necessary, and no earlier than after 4 weeks, a NSAID was added. Our preferential order being naprosyn 500 mg twice a day, followed by substitution of meloxicam 15 mg once a day or ibuprofen 600 mg three times a day at Week 8 when necessary (Step 3). Step 4 includes substitution of the NSAID for tramadol (50 mg three times a day). For patients with an NRS pain ≤ 4 at baseline, all modalities of the protocol were offered, but no new analgesics were prescribed.

**Measurement instruments**

**Fatigue**

Fatigue was assessed by the Checklist Individual Strength (CIS) [21]. This 20-item patient-assessed questionnaire consists of four subscales: (i) fatigue severity (CIS fatigue, eight items, range 8–56, for example, ‘I feel tired’); (ii) reduction in concentration (CIS concentration, five items, range 5–35, for example, ‘My thoughts easily wander’); (iii) reduction in motivation (CIS motivation, four items, range 4–28, for example, ‘I feel no desire to do anything’); and (iv) reduction in physical activity (CIS activity, three items, range 3–21, for example, ‘I don’t do much during the day’). Each item is scored on a 7-point Likert scale. Furthermore, CIS fatigue was divided into three classes: (i) normal experience of fatigue (normal fatigue; score <27) (mean score for healthy controls plus one s.d. [22]); (ii) moderate experience of fatigue (moderate fatigue; score 27–34); and (iii) severe experience of fatigue (severe fatigue; score ≥35) (scores comparable with fatigue as experienced by patients with chronic fatigue syndrome) [21]. The CIS has proven to be a reliable and valid instrument in various conditions [22–24].

**Pain, patient global assessment, stiffness and physical functioning**

To measure pain, stiffness and daily functioning, the Likert scale version of the knee/hip injury and OA outcome score (KOOS/HOOS) questionnaire was used. KOOS/HOOS questionnaires include the Western Ontario McMaster Universities OA index (WOMAC) in its complete and original format (with permission, http://www.koos.nu). WOMAC pain, stiffness and function subscales were calculated (0–100, where 0 equals no symptoms). In addition, patient global assessment (PGA) of OA severity was measured using an NRS (0–10).

**Radiographs**

Bilateral (posterior–anterior, fixed flexion and lateral) knee and pelvic radiographs were performed in all participants [25]. The joint with the most complaints at baseline was graded according to the Kellgren–Lawrence grading scale (K&L score) [26]. All radiographs were read by an experienced rheumatologist and/or a trained research physician (G.F.S.).

**Data collection and management**

Demographics, radiographs, and data on previously used treatment modalities concerning knee and/or hip OA and data on symptoms were obtained in all patients. Questionnaires were collected at baseline and after 12 weeks.

**Statistics**

Statistical analyses were performed using STATA/IC 10.1 for Windows. In patients with incomplete baseline or follow-up data, multiple imputations were performed using regression modelling to replace missing values. Descriptive statistics were provided. Levels of fatigue before and after 12 weeks of treatment were compared using a χ²-test (for nominal variables), a paired t-test or Wilcoxon’s signed-rank test (for continuous variables, depending on distribution). The subscale CIS fatigue was divided into three classes as mentioned previously. Effect sizes (ESs) were, when applicable, calculated using the following formula: difference between mean before and mean after the intervention divided by the s.d. of the variable.

Although pain and physical function were relatively highly correlated (r = 0.83), the variance inflation factor (VIF) indicated no problematic multicollinearity (VIF = 3.2).

Association models were built with one of the fatigue dimensions as the dependent variable and both pain (WOMAC pain) and physical function (WOMAC function) as central determinants. Regarded as potential confounders were age, gender, BMI, index joint (knee or hip), duration of complaints, K&L score and past treatment. The variables were added to the model one by one to test for possible confounding (cutoff for relevant change in the regression coefficient (β) of daily functioning and pain was ≥10%). The same procedure was followed to study the association of change in fatigue after 12 weeks (dependent variable) with change in pain and daily functioning as central determinants. All models were checked for heteroscedasticity and non-normality of residuals using visual inspection of residual plots.

**Results**

Between April 2008 and February 2010, 292 knee and/or hip OA patients fulfilled inclusion criteria, of which 231 had sufficient follow-up data (Table 1). The main reason for insufficient data was loss of follow-up. No clinically relevant baseline differences were found between patients with and without sufficient follow-up data.

Data regarding CIS subscales are depicted in Table 2. Patients with knee and/or hip OA in our study experienced significantly more fatigue in two dimensions (CIS fatigue and CIS activity) compared with data on healthy controls from the literature (31.8 vs 17.3 and 12.1 vs 6.6, respectively) [24, 27]. A total of 28 of 231 participants (12%) received only non-pharmacological treatment during the 12-week treatment period, whereas all other individuals had at least one additional pharmacological intervention.
At the group level, there was a small (significant) decrease in CIS fatigue and CIS activity after 12 weeks of evidence-based tailored conservative treatment. At baseline, 109 patients (47%) met the criteria for severe fatigue (i.e. CIS fatigue ≥35), and this decreased to 85 patients (37%) after 12 weeks. After 12 weeks of evidence-based tailored conservative treatment improvements in NRS pain [from 5.9 to 4.9, $P < 0.001$, effect size (ES) = 0.48], WOMAC pain (from 53 to 47, $P < 0.001$, ES = 0.27) and physical function (from 54 to 47, $P < 0.001$, ES = 0.31) were found.

In the cross-sectional model (Table 3), physical function was independently associated with CIS fatigue at baseline. Pain was not independently associated with CIS fatigue. Physical function was also independently associated with CIS activity at baseline. For the cross-sectional model, no confounders were identified.

In the longitudinal model (Table 4), change in CIS fatigue after 12 weeks of conservative treatment was not associated with baseline physical function and pain levels. However, change in CIS fatigue was independently associated with improvement of physical function. No confounders could be identified for this relation. Change in CIS fatigue was not associated with improvement of pain. Change in CIS activity after 12 weeks of conservative treatment was not associated with baseline physical function and pain levels. However, change in CIS activity was independently associated with improvement of pain and physical function. No confounders could be identified for this relation.

Discussion

The results of the current study show that levels of fatigue severity, and to a lesser extent physical fatigue, are high in patients with well-characterized knee and hip OA, with nearly half of the patients experiencing severe fatigue. Evidence-based tailored conservative treatment resulted in a small decrease in experienced fatigue. Reduction of fatigue severity was found to be related to physical function, whereas reduction of physical fatigue seemed to be related to the level of physical function and pain. To our

Table 1 Baseline characteristics of patients ($n = 231$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>150 (65)</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>54 (10)</td>
</tr>
<tr>
<td>BMI, median (p25–75)</td>
<td>28 (25–32)</td>
</tr>
<tr>
<td>Knee OA, n (%)</td>
<td>192 (83)</td>
</tr>
<tr>
<td>Duration of knee or hip complaints, median (p25–75), years</td>
<td>4 (2–11)</td>
</tr>
<tr>
<td>K&amp;L score ≥ 2, n (%)</td>
<td>128 (56)</td>
</tr>
<tr>
<td>Past treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Analgesics</td>
<td></td>
</tr>
<tr>
<td>Paracetamol in adequate dose$^a$</td>
<td>62 (27)</td>
</tr>
<tr>
<td>One or more NSAIDs</td>
<td>158 (68)</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>148 (64)</td>
</tr>
<tr>
<td>NRS pain (0–10), mean (s.d.)</td>
<td>5.9 (2.1)</td>
</tr>
<tr>
<td>NRS PGA (0–10), mean (s.d.)</td>
<td>6.3 (2.2)</td>
</tr>
<tr>
<td>WOMAC pain (0–100), mean (s.d.)</td>
<td>53 (22)</td>
</tr>
<tr>
<td>WOMAC stiffness (0–100), mean (s.d.)</td>
<td>57 (24)</td>
</tr>
<tr>
<td>WOMAC function (0–100), mean (s.d.)</td>
<td>54 (23)</td>
</tr>
</tbody>
</table>

Higher scores indicate poorer outcome unless stated otherwise. $^a$Adequate dose: 1000 mg 2-4 times/day during at least 14 consecutive days. Paracetamol: paracetamol acetaminophen.

Table 2 Levels of fatigue dimensions before and after standardized conservative treatment ($n = 231$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Change (95 % CI)</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS fatigue</td>
<td>31.8 (13.6)</td>
<td>30.2 (13.6)</td>
<td>−1.6 (−0.3, −3.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>CIS concentration</td>
<td>13.8 (8.1)</td>
<td>13.1 (7.8)</td>
<td>−0.8 (−1.6, 0.07)</td>
<td>−</td>
</tr>
<tr>
<td>CIS motivation</td>
<td>11.9 (6.2)</td>
<td>11.3 (5.6)</td>
<td>−0.6 (−1.3, 0.06)</td>
<td>−</td>
</tr>
<tr>
<td>CIS activity</td>
<td>12.1 (5.5)</td>
<td>11.1 (5.6)</td>
<td>−1.0 (−0.4, −1.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Severe fatigue$^a$, %</td>
<td>47.2</td>
<td>36.8</td>
<td>−10.4</td>
<td></td>
</tr>
<tr>
<td>Moderate fatigue$^a$, %</td>
<td>19.1</td>
<td>22.9</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Normal fatigue$^a$, %</td>
<td>33.8</td>
<td>40.3</td>
<td>6.5</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are mean (s.d.) unless stated otherwise. $^a$CIS fatigue was divided into three classes: normal fatigue (CIS fatigue < 27), moderate fatigue (CIS fatigue 27–35) and severe fatigue (CIS fatigue ≥ 35).

Table 3 Cross-sectional association model with baseline fatigue scores as dependent variables and WOMAC subscales as central determinants

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS fatigue</td>
<td></td>
</tr>
<tr>
<td>WOMAC function</td>
<td>0.38 (0.27, 0.50)</td>
</tr>
<tr>
<td>WOMAC pain</td>
<td>−0.08 (−0.20, 0.04)</td>
</tr>
<tr>
<td>$R^2 = 0.29$</td>
<td></td>
</tr>
<tr>
<td>CIS activity</td>
<td></td>
</tr>
<tr>
<td>WOMAC function</td>
<td>0.14 (0.08, 0.19)</td>
</tr>
<tr>
<td>WOMAC pain</td>
<td>−0.06 (−0.11, 0.01)</td>
</tr>
<tr>
<td>$R^2 = 0.16$</td>
<td></td>
</tr>
</tbody>
</table>

Bold indicates an independent association with CIS fatigue/activity.
knowledge, this is the first study to evaluate the impact of recommended medical treatment on different dimensions of fatigue in symptomatic OA.

Our study confirms that fatigue, and even severe fatigue, is highly prevalent among patients with knee and/or hip OA. This is not only true for fatigue severity, but also for physical fatigue. Motivational fatigue and concentration, however, are not affected. Of note, direct comparison of CIS subscale levels in the present study and levels in healthy controls is difficult, since the latter consisted of 53 healthy individuals (mean age 31.1 years, s.d. 11.5) matched with patients with chronic fatigue syndrome and multiple sclerosis [24]. However, also by indirect comparison, it can be assumed that OA patients experience more fatigue (measured with the CIS) than healthy persons, as levels of CIS fatigue in our OA cohort are quite similar with levels in RA patients, and RA patients are known to have increased fatigue levels.

The findings in our study are in line with the sparse existing data on fatigue in OA [2, 4, 5] and underscore that fatigue is indeed an important issue in patients with OA. Measured levels of fatigue are comparable with levels seen in inflammatory rheumatic diseases such as RA [3-5, 11, 12, 28] and AS [29] and somewhat higher than observed in PsA [30].

It should be noted that no control group was used, therefore bias by, for example, regression to the mean or placebo effect cannot be ruled out. To our knowledge only one other longitudinal study that assessed fatigue after standardized treatment in OA has been published. This randomized controlled trial assessed the effect of a self-management programme in knee OA patients and found no significant decrease in fatigue and physical function after 12 months, whereas pain decreased significantly [31]. This is in line with the results from the present study indicating that fatigue severity is related to improvement of physical function and not to pain.

Regarding the underlying mechanism of fatigue in OA, our data suggest that fatigue severity is partly determined by physical function, whereas physical fatigue is determined by both physical function and pain. These associations were found in both our cross-sectional as well as our longitudinal analyses. As our standardized treatment included interventions explicitly targeting pain and physical function, including lifestyle advice, physical therapy and analgesics, we may conclude that the direction of causality is that a decrease in physical function induces more severe fatigue and a decrease in pain, in addition increasing in physical function, improves physical fatigue. The finding that different dimensions of fatigue in rheumatic diseases have different determinants has not yet been demonstrated. A recently published prospective cohort study indicated that fatigue is determined by physical function [8], which is in concordance with our study.

In this study, no confounders were identified. However, fatigue certainly depends on other non-measured variables (e.g. psychosocial factors), as indicated by the low to moderate explained variance that was found. Furthermore, the present study was primarily set up to investigate the relation between fatigue and physical function and between fatigue and pain, because these are the main domains targeted in conservative treatment of OA.

The study cohort that was used—symptomatic knee and hip OA in secondary care—is comparable with other cohorts, consisting mainly of obese women with knee OA [32, 33]. However, the level of pain and BMI were higher and patients were younger, possibly reflecting selection of a cohort with relatively high levels of complaints. However, this should not lead to biased inferences.

Future research should be directed to answer several important remaining questions. Although the decreases in levels of fatigue after evidence-based tailored conservative treatment are only modest, it is possible that the maximum effect of the intervention is not yet reached after 12 weeks. Another explanation for the fact that only a moderate effect on fatigue was found could be that individuals with high levels of experienced fatigue are probably unwilling to attend physical therapy or change their lifestyle. Besides, it could be presumed that a more intensive multidisciplinary approach to improve function and pain will result in a more substantial decrease in fatigue levels. Furthermore, given the relatively low ES found, an approach especially targeted to reduce fatigue will have much greater effects. To realize this, more insight is required into the underlying mechanisms regarding fatigue in OA, with, for example, depression and sleep disturbances [34] being potential causal factors. Targeting these domains could potentially reduce fatigue levels in OA.

In summary, high levels of fatigue are very common in knee and hip OA and are associated with physical function and pain. Evidence-based tailored conservative treatment targeted at improvement of physical function and pain also leads to a small reduction in fatigue levels, with a change in fatigue severity being related to physical function and a change in physical fatigue being related to pain and physical function.
Fatigue in knee and hip OA

Rheumatology key messages

- Important levels of fatigue are common in knee and hip OA.
- Treatment targeted to improve physical function and pain results in small reductions of fatigue levels.
- Levels of affected fatigue dimensions are related to changes in physical function and pain.

Acknowledgements

We thank Dr D.J.R.A.M. de Rooij for radiograph scoring, V.H.H.P. Straten for data collection, Dr F.H.R. de Man for patient referral and F.W. Snijders, N.W.D. Eikelenboom and N. den Broeder for data entry and data management.

Disclosure statement: The authors have declared no conflicts of interest.

References


25 Peterfy C, Li J, Zaim S et al. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee:


