REVIEW ARTICLE

Factors Associated With Generalised Fatigue Among Individuals With Knee Osteoarthritis: A Systematic Review

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ABSTRACT

This review aimed to investigate the factors associated with generalised fatigue among individuals with knee osteoarthritis. An extensive literature search was performed in Cumulative Index of Nursing and Allied Health Literature, ClinicalKey, Pubmed, Scopus and Web of Science for observational studies, available in Chinese, English or Malay language, evaluating generalised fatigue and its associated factors among individuals with clinically or radiologically diagnosed knee OA from inception up to November 2020. Five studies met the inclusion criteria and their methodological quality was appraised using the National Heart, Lung and Blood Institute quality appraisal tool. Although high quality studies reported the comorbidities, higher mental tasks, lower physical activity levels and physical function associated with fatigue, conflicting evidence indicated poor sleep quality, depression and pain associated with fatigue. The limited factors identified for generalised fatigue among individuals with knee OA thus warrant future research.

Keywords: : Knee osteoarthritis, Fatigue, Associated factors, Systematic review

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INTRODUCTION

Fatigue is characterised as a feeling of constant exhaustion or tiredness (1). It is a common symptom in chronic diseases like osteoarthritis (OA), fibromyalgia, ankylosing spondylitis, rheumatoid arthritis (RA) and systemic lupus erythematosus (2,3). Around 50% of adults suffering from OA reported generalised fatigue (4). Fatigue has a prevalence of 41% in people with OA or RA (5) and 47% in those with hip or knee OA (6). Moreover, its prevalence solely among knee OA individuals is reported to be as high as 81.5% (7). Individuals aged 65 years and above experience fatigue fourfold higher than do healthy individuals (4,8). Fatigue impacts a person's functional performance, social life and most of the daily living activities of individuals with OA (9). Hence, fatigue is a major key factor in decreased quality of life (QoL) (10) and substantial disability in individuals with knee OA (11,12).

Factors believed to raise the level of fatigue among individuals with OA include aging, pain, analgesic medications, cold weather and poor sleep quality (9). Arthritis pain, comorbidities, female gender, depression, disability, low levels of physical activity, poor physical function (13) and increased demand for mental activities were also suggested as correlates of fatigue (14). The increased fatigue level is associated with a decline in the level of physical activity (10) and poor life quality among individuals with knee OA (12).

Despite the adverse consequences of fatigue and its high prevalence in individuals with knee OA, the pathology of fatigue remains unclear owing to its complexity and multifactorial characteristics (15). There is also no standardised definition of fatigue among individuals with knee OA (16). Furthermore, fatigue in knee OA has received less attention relative to other chronic inflammatory diseases such as RA (17). The assessment of fatigue has also been neglected in the provision of OA care (9). In individuals with knee OA, fatigue received less attention due likely to the fact that previous studies assessing fatigue in OA involved participants with other rheumatic conditions (5,18); mixed populations with contrasting OA conditions like OA of the hip, knee and/or hand (5,6,19); or often used other clinical populations like fibromyalgia and RA, which constituted a small proportion of individuals with knee OA (5, 19-21).

More information about the prevalence of fatigue and its related factors in knee OA is needed to emphasise the evaluation and prevention of fatigue in knee OA. Until now, fatigue in knee OA has received relatively

limited attention, and there is no comprehensive list of factors associated with fatigue in knee OA. Thereby, the main objective of this review was to examine the factors associated with generalised fatigue among individuals with knee OA. With such an overview, fatigue can be better understood and managed by incorporating these factors in OA assessment and treatment plans. The findings of the study would be relevant to researchers, clinicians, physiotherapists and everyone who could be a member of the team providing health care to individuals with knee OA.

MATERIALS AND METHODS

Data Sources

A comprehensive search was conducted in the relevant medical databases from inception to November 2020: CINAHL, ClinicalKey, Pubmed, Scopus and Web of Science. Additionally, the reference lists of all relevant identified studies were retrieved and screened for further possible relevant articles, and Google Scholar was sought to find additional papers.

Search Strategy

The search strategy for the literature search was established in PubMed after consulting the librarian and modifying the strategy for use in other relevant databases. The full search strategy as formulated in PubMed is ('Osteoarthritis, knee' [MeSH Terms] OR Knee osteoarthritis [tw]) AND ('Fatigue' [MeSH Terms] OR ' Fatigabilty' [tw] OR 'Lethargy' [tw] OR ' Tiredness' [tw] OR 'Exhaustion' [tw]).

Selection of Studies

Studies were selected according to inclusion and exclusion criteria. The inclusion criteria were as follows: full-length observational studies published in English, Chinese or Bahasa Malaysia; available from inception to November 2020; evaluating fatigue and its associated factors among participants with the physician diagnosis or radiological assessment based on Kellgren and Lawrence classification of knee OA. The exclusion criteria were as follows: studies with combined populations, (i.e. knee OA with multiple OA conditions such as hip OA and hand OA, other rheumatic conditions such as RA and any other conditions like fibromyalgia, etc.). Initially, the studies were evaluated based on the title and then the abstract. Finally, the full text of the relevant studies was reviewed. It was decided by the authors to consider a associated factor of fatigue if it was found in one or more studies.

Quality Assessment

The methodological consistency of each study was assessed by using the National Heart, Lung and Blood Institute (NIH) quality appraisal tool for Observational Cohort and Cross-Sectional Studies (22). This tool consists of 14 questions, and each question has three options: Yes, No and Other (CD: cannot determine, NA: not applicable and NR: not reported). The quality rating of the study is to be reported as good, fair or poor depending on their scoring (23). A good-quality research was thought to have a low risk of bias (ROB), a fair-quality study to have moderate ROB and a poor-quality study to have moderate ROB (23). The overall score of a study was the percentage score of all 14 items. A study with an overall score of more than 60% was supposed to be a high-quality study and less than 60% score as a low-quality study (24).

Data Extraction

Relevant data from all eligible studies were extracted from each study: authors of the study, study design, sample size, target population, fatigue assessment and, finally, conclusion of study.

Best Evidence Synthesis

The studies had heterogeneous methodological quality, so the best evidence synthesis was employed to rank the levels of evidence (24,25). Firstly, the studies were categorised into types of study designs, namely longitudinal and cross-sectional. Next, the studies were ranked according to the methodological quality score based on the NIH tool.

RESULTS

Characteristics of Included Studies

The flow for the literature search is presented in Fig.1. The final search strategy yielded 14 eligible studies; after the full-text screening, 5 studies (7,12,15,16, 26) met all the inclusion criteria. Three studies had a cross-sectional design and two had a longitudinal study design. The characteristics of all five studies have been presented in Table I.

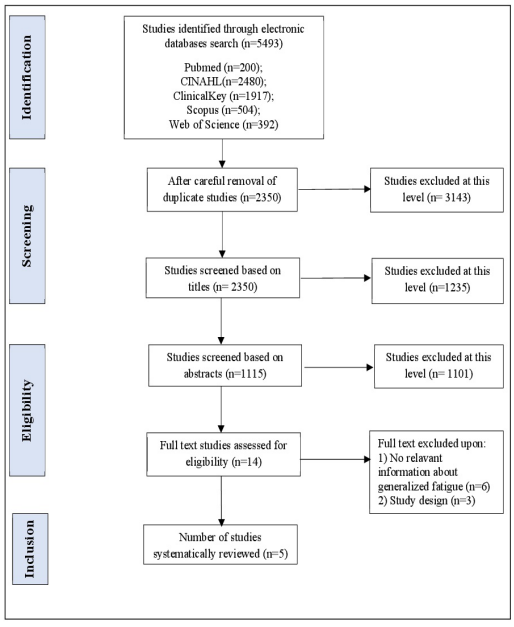

Fig 1: Study selection of flow chart

Table I. Overview of the characteristics of the five studies.

Citation	Study design	Study population	Sample size	Fatigue Assessment	Conclusion	Quality Score
Fertelli &Tuncay (2019)[1]	Cross-sectional	Physician diagnosed individuals with knee OA	151 with knee OA 147 healthy individuals	Visual analogue scale for fatigue (VAS-F)	Individuals with knee OA had higher level of fatigue and a positive correlation was found between fatigue, sleep quality, depressive symptoms and pain.	57%
Fawole et al. (2020)	Longitudinal study	Radiological diagnosed individuals with knee OA based on Kellgren and Lawrence system	449 with sympotomatic knee OA 1260 without symptomatic knee OA	VAS-F	In individual with symptomatic knee OA baseline fatigue, depressive symptoms, poor aleep quality, pain, physical function (i.e gait speed) and comorbidities were found significant predictor of fatigue during follow up over 2 years period of study	78%
Garip, Guler & Tuncer (2016)	Cross-sectional	Radiological diagnosed individuals with knee OA based on Kellgren and Lawrence system	80	Fatigue symptom Inventory (FSI)	Fatigue was found strongly correlated with pain and depression. Moreover the intensity and duration of fatigue was found associated with poor quality of life	43%
Fawole et al. (2020)	Longitudinal study	Self reported doctor diagnosed individuals with knee OA	23	Numerical rating scale 0-10	Cognitive control for mental tasks demands energy and effort that cause fatigue and decrease physical particpation which further incraese fatigue	78%
Smith & Parmelee (2016)	Cross-sectinoal	Physicain diagnosed individuals with knee OA	120	7 days ESM Protocol	Fatigue was found a significant factor among individuals with knee osteoarthritis. Pain was found a strong predictor of fatigue and an assoctaion between race and fatigue was aslo reporeted	57%

Methodological Quality

Three reviewers independently assessed the methodological quality of each included study. While scoring the methodological quality of each study, the reviewers had some initial disagreements. However, during a later meeting, it was found that nearly all disagreements were either due to reading errors or a different interpretation of some questions of the NIH tool. Finally, at the end of the meeting, there was no longer any disagreement. On the basis of the quality score percentage, two studies were ranked as high quality (15,16) and three studies were ranked as low quality (7,12,26). The total scores of methodological quality of the five included studies are displayed in Table II.

Associated Factors of Fatigue

Certain factors associated with fatigue in knee OA were discovered, including lower levels of physical activity, pain, depression, poor sleep quality, race, higher mental tasks, poor physical function, comorbidities and poor physical function. There was limited evidence found that lower physical activity levels, higher mental tasks, comorbidities and poor physical function are associated with fatigue in knee OA. Conflicting evidence was likewise observed for depression, pain and poor sleep quality as associated factors of fatigue. In addition, there was insufficient evidence documented that race and poor QoL are associated factors of fatigue. The evidence level for each associated factor has been illustrated in Table III.

DISCUSSION

The key focus of this review was to outline the associated factors of fatigue among individuals with knee OA. Hence, we investigated the current evidence about fatigue and its associated factors mainly among individuals with knee OA. After a systematic literature search, only five studies were selected, three of which had a cross-sectional design (7,12,26) and two with an extensive longitudinal design (15,16). The comprehensive interpretation of all these five studies helped identify the factors related to

Table II. Quality assessment and risk of bias (ROB) summary on the basis of NIH* Tool

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Scoring	Quality Rating	ROB
Fertelli &Tuncay (2019)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	N/A	N/A	N/A	8	Fair	Moderate
Fawole et al. (2020)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	11	Good	Low
Garip, Guler & Tuncer (2016)	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	No	No	No	6	Poor	High
Fawole et al. (2020)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	11	Good	Low
Smith & Parmelee (2016)	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	8	Fair	Moderate

*NIH: National Heart, Lung and Blood Institute quality appraisal tool (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Q1: Q1: Research question/objective, Q2: Study population, Q3: Participation rate, Q4: Inclusion criteria, Q5: Sample size justified, Q6: Exposure prior to outcome, Q7: Sufficient timeframe, Q8: Different level of exposure, Q9: Exposure measure, Q10: Multiple exposure measurement, Q11: Outcome measure, Q12: Blinding of outcome assessor, Q13: Loss of follow up,Q14: Potential confounding.

Table III. Overview of the factors associated with fatigue in individuals with knee OA.

Associated factors	Association found	Association not found	Level of evidence
Pain	One high-quality longitudinal study 3 low-quality cross-sectional studies	One high-quality longitudinal study	Conflicting evidence
Sleep quality	One high-quality longitudinal study One low-quality cross-sectional study	One high-quality longitudinal study 2 low-quality quality cross-sectional studies	Conflicting evidence
Quality of life	One low-quality cross-sectional study	2 high-quality longitudinal studies 2 low-quality cross-sectional studies	Insufficient evidence
Depression	One high-quality longitudinal study 2 low-quality cross-sectional studies	One high-quality longitudinal study One low-quality cross-sectional study	Conflicting evidence
Physical activity levels	One high-quality longitudinal study	One high-quality longitudinal study 3 low-quality cross-sectional studies	Limited evidence
Physical function	One high-quality longitudinal study	One high-quality longitudinal study 3 low-quality cross-sectional studies	Limited evidence
Race	One low-quality cross-sectional study	2 high-quality longitudinal study 2 low-quality cross-sectional studies	Insufficient evidence
Mental task	One high-quality longitudinal study	One high-quality longitudinal study 3 low-quality cross-sectional studies	Limited evidence
Comorbidities	One high-quality longitudinal study	One high-quality longitudinal study 3 low-quality cross-sectional studies	Limited evidence

fatigue, such as pain, poor sleep quality, depression, poor QoL, lower physical activity levels, poor physical function, race, higher mental tasks and comorbidities among individuals with knee OA.

Limited Evidence

There is limited evidence found regarding poor physical function, comorbidities, lower levels of physical activity and higher mental tasks as associated factors of fatigue. A longitudinal study identifying the determinants of general fatigue in individuals with knee OA revealed that poor physical function such as slow gait speed is strongly associated with fatigue. The authors proposed that slow gait speed, a measure of physical deconditioning, contributes to fatigue and vice versa, creating a vicious circle in which less physical function or difficulties

in completing everyday tasks increases physical deconditioning, which provokes fatigue (15). The same association between poor physical function and fatigue had been reported in previous studies, but these studies measured other constructs of fatigue (tiredness and vitality) (12,27). A longitudinal study determining the temporal association between mental activity, physical activity and different fatigue dimensions (general, physical and mental fatigue) suggested that generalised fatigue is linked to lower physical activity levels. The study suggested that an increase in general fatigue lowers the energy levels, which in turn cause a drop in physical activity level (16). Individuals with generalised fatigue prefer to rest and minimise physical activities to overcome fatigue, which in turn has a detrimental effect on their health as they already have low physical activity levels (28,29). Thus, overcoming general fatigue can have a clinically important effect on the physical activity level and overall health of individuals with knee OA (16).

While evaluating the determinants of fatigue in a two-year follow-up study, a longitudinal study found a significant association between comorbidities and fatigue in individuals with knee OA. The present study suggested that comorbidities might influence health and reduce physical performance, which will likely cause fatigue (15). The presence of comorbidities, like musculoskeletal or non-musculoskeletal disorders, sensory impairment and higher body mass index, has been confirmed in existing literature to have a high prevalence (28) of 66%–68% in individuals with OA (31–33).

A longitudinal study evaluating the physical and mental dimension of fatigue in individuals with knee OA suggested that exerting cognitive control for different mental activities demands energy and effort, which eventually drops the energy level in body. The decrease in energy level causes a feeling of exhaustion in the body that leads to a decrease in physical activity level and lethargy, which may further intensify fatigue level and thus develop into a vicious circle (16).

Conflicting Evidence

There is conflicting evidence that fatigue is related to pain, poor sleep quality and depression among individuals with knee OA. A cross-sectional study reported a strong relationship between severity of pain and fatigue, which might be due to an etiological relationship between fatigue and pain (12). The findings of this study were consistent with a previous study in which fatigue was studied among individuals with knee OA along with other populations like RA and fibromyalgia (21). The results of the other two cross-sectional studies showed that fatigue and pain can affect each other and have a positive relationship (7,26). This result was similar to those of previous studies (10,12,33,34). A longitudinal study conducting bivariate and multivariate analyses of associated factors of fatigue found that pain and baseline fatigue had a significant association in the bivariate model, but this association was diminished in multiple regression models during the two-year follow-up period of the study. One possible explanation is that they used baseline fatigue in their bivariate model because it is likely that baseline fatigue is associated with pain. Similarly, high levels of fatigue at follow-up in certain individuals with low levels of pain in bivariate analysis could explain why the relationship between pain and fatigue declined over the period of study (15). The findings of the present study were consistent with a previous study (6) but differed from another study that found pain to be a predictor of fatigue even over a two-year study (35). This difference was likely due to the difference in pain intensity and fatigue measurement scales used in both studies (15).

In two cross-sectional studies, fatigue was found to be strongly correlated with depression in individuals with knee OA (7,12). The studies suggested that depression significantly affects pain symptoms, which in turn cause patients to experience more fatigue; thus, there is a positive relationship between fatigue and depression (7). The findings of these two studies were found to be consistent with the results of previous studies (9,17,21,34,36). Furthermore, a longitudinal study suggested that depression is a modifiable associated factor of fatigue and proposed that reducing depression can predict significant fatigue improvement (15).

A cross-sectional study observed that a positive relationship between poor sleep quality and fatigue exists along with pain and depression and it was also suggested that managing sleep disturbances would be a significant strategy to overcome fatigue among individuals with knee OA (7). These findings agreed with previous studies that individuals with knee OA experienced sleep disturbance that is somehow linked to fatigue which needs to be emphasized (12,17,36).

A longitudinal study found that there is a strong correlation between poor sleep quality and fatigue in a bivariate model that was no more significant in multivariable analysis. This weak relationship might be due to the inclusion of other variables like depressive symptoms and baseline fatigue (15). The contrasting findings regarding fatigue and sleep quality among other rheumatic populations such as RA might be attributed to different construct, measurement tools, and follow-up times used in previous studies (37-39). So more longitudinal studies are recommended to look over the effect of sleep quality on fatigue and appropriate measure of sleep in the population with knee OA which would be polysomnography (15).

Insufficient Evidence

Insufficient evidence was found for the association of poor life quality and race with fatigue. A cross-sectional

study found that poor QoL was associated with intensity and duration of fatigue in terms of pain, physical function and mobility, sleep, energy and psychological function (sub-group of QoL). However, the social function (a subgroup of QoL) had no link with fatigue, which might be due to the gender of their study population mainly being female. These females had very simple activities that usually caused no fatigue, and hence the social function domain had no association with fatigue (12). Their findings were found to be similar to previous studies among individuals with knee OA, along with other populations such as hip OA and other arthritic conditions (5,9,34). A cross-sectional study comparing fatigue experiences among two races (African American and non-Hispanic Americans) with knee OA found that both groups experienced a moderate rate of fatigue (26). Surprisingly, an increase in fatigue level was higher in the non-Hispanic Americans compared to the African-American group throughout the day. The authors suggested that this difference could be attributed to the different sorts of activities adopted by the two groups throughout the day. However, future studies are recommended to ensure whether the racial difference of fatigue symptom patterns throughout the day exist or not (26).

This review has a few limitations that need to be addressed. Firstly, this review just focused on a specific domain of fatigue (general fatigue). The other domains of fatigue common among individuals with knee OA, like mental and physical fatigue, specifically muscle fatigue (quadriceps and hamstring muscles), could also be addressed. Secondly, the relevant studies used only the subjective measurement of fatigue. There could be more accurate measures of fatigue, such as a 6-minute walk test and so forth. Thirdly, there could be better and different choices for the methodological quality appraisal tools for each study type (i.e. cross-sectional and longitudinal study) rather than choosing a single tool for both study types.

CONCLUSION

According to the findings of this review, limited evidence was found for the association of fatigue with lower physical activity levels, poor physical function and higher mental tasks and comorbidities. Depression, pain and poor sleep quality were listed in the conflicting evidence category while there was insufficient evidence to support the association of low life quality and race with fatigue. The findings of this review will be used clinically to assist healthcare providers in identifying and managing the associated factors of fatigue among individuals with knee OA. These associated factors such as comorbidities, higher mental tasks, lower physical activity levels and physical function can be targeted as early as possible in order to minimise the fatigue. There was a lack of high-quality studies in this regard. Out of the five studies, only two were of high quality. Thereby, this review did not present strong or even moderate evidence considering the prevalence of fatigue and its associated factors among individuals with knee OA. As a result, future longitudinal studies with well-defined populations, particularly individuals with knee OA, are needed.

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