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Review article

A review and synthesis of correlates of fatigue in osteoarthritis

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ABSTRACT

Fatigue affects nearly half of all adults with osteoarthritis. Affected individuals report difficulty with daily functioning, requiring more time and rest during activities, feeling easily exhausted, and having to give up on social and volunteer activities known to improve quality of life. Because its etiology is poorly understood, clinical practice guidelines are unable to address management of fatigue in osteoarthritis. Elucidating a mechanism of osteoarthritis fatigue is a high priority, but few studies have identified key factors associated with fatigue in osteoarthritis. Thus, the purpose of this narrative literature review is to present the current evidence of known and potential correlates of fatigue in osteoarthritis, and synthesize our findings into a conceptual framework. The overarching goal of this work is to provide insight into areas of needed research and guide future work toward mechanistic insight of osteoarthritis fatigue. This knowledge could lead to novel nursing interventions for prevention, management, and treatment of fatigue among adults with osteoarthritis.

Introduction

Osteoarthritis affects over 30 million adults in the United States (Centers for Disease Control and Prevention, 2017). Older adults are most commonly affected; with the average age of diagnosis between 50 and 53 years (Berger et al., 2011; Losina et al., 2013; Macdonald et al., 2014). Arthritis, including osteoarthritis, is a leading cause of disability in the United States (Centers for Disease Control and Prevention, 2013). Osteoarthritis is characterized by a degeneration of joint cartilage and underlying bone accompanied by symptoms of pain, joint stiffness, and fatigue (Wyatt et al., 2014). Between 35 and 41% of adults with osteoarthritis report severe or clinically significant fatigue (Overman et al., 2016; Wolfe et al., 1996). While pain has been considered the primary contributor to disability in osteoarthritis (Huang et al., 2015; Leveille et al., 2002), mounting evidence suggests that fatigue is also independently associated with osteoarthritis related disability (Garip et al., 2016; Murphy et al., 2008; Novaes et al., 2011; Sturgeon et al., 2015).

Fatigue is defined in many ways, and research outside of osteoarthritis suggests it is a multidimensional concept. Yet, in osteoarthritis, fatigue is not well explored or defined. For the purposes of this discussion we refer to osteoarthritis fatigue as generalized fatigue and define it as "an overwhelming, debilitating, and sustained exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles" (Riley et al., 2010, p.1318, p.1318). Specifically, adults with osteoarthritis describe fatigue as "complete exhaustion" and feeling like "coming up against a brick wall" (Power et al., 2008), that is similar (Chua et al., 2017; Wolfe et al., 1996; Wolfe et al., 2004) or worse when compared to the fatigue experienced by adults with rheumatoid arthritis (Chua et al., 2017; Cross et al., 2008; Zautra et al., 2007).

Fatigue in community-dwelling older adults is associated with greater mortality over ten years (Hardy and Studenski, 2008), a risk that may also exist in osteoarthritis fatigue. The magnitude of the association between fatigue and mortality in older adults is similar to that seen in heart disease and diabetes mellitus (Hardy and Studenski, 2008). In addition to potential increased mortality, fatigued adults with osteoarthritis have difficulty with physical activity and function like walking, exercising, and performing chores, and need to take more time, require more rest, and are easily exhausted as compared to adults with rheumatoid arthritis or when symptoms of fatigue were not present (Cross et al., 2008; Power et al., 2008). Moreover, adults with osteoarthritis fatigue report having to give up volunteer and social

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activities, which are essential for maintaining joint function and life engagement for successful aging (Power et al., 2008).

Despite the significant burden fatigue places on adults with osteoarthritis, limited interventions exist to mediate it. The Agency for Healthcare Research and Quality's national clinical guidelines for care and management in adults with osteoarthritis do not address management of fatigue (National Clinical Guideline Centre, 2014). Moreover, the Arthritis Foundation recommends treatment of underlying conditions (e.g., anemia, malnourishment) to treat fatigue, but make only lifestyle recommendations (e.g., increased physical exercise, adequate hydration) for management of generalized fatigue without a clear underlying cause (Arthritis Foundation, n.d.). An understanding of the underlying causes of fatigue among adults with osteoarthritis is necessary for establishing effective treatments and improving quality of life. To begin to illuminate potential mechanisms for fatigue in osteoarthritis, we first must be aware of correlates of fatigue in osteoarthritis. Thus, the purpose of this narrative literature review is to present the current evidence of known and potential factors associated with fatigue in osteoarthritis, and synthesize the findings into a conceptual framework. The overarching goal of this work is to provide insight into areas of needed research and guide future work toward mechanistic insight of osteoarthritis fatigue.

Methods

Typically, the most robust way to synthesize research on a topic like osteoarthritis fatigue is to conduct a systematic review. A systematic review uses a rigorous and methodical protocol to search for, select, appraise, and synthesize primary research to provide unbiased research findings (Queensland University of Technology, 2018). However, because there is limited research to pool together for conducting a systematic review, a narrative literature review of this topic was performed. A narrative literature describes and discusses the state of the science of a specific topic from a theoretical or conceptual framework (Systematic literature review x narrative literature review, 2007). Thus, a narrative literature review as conducted as an important first step in encouraging work in this area of osteoarthritis.

First, a literature search was conducted in PubMed and CINAHL using search terms that included: “osteoarthritis”, “fatigue”, “correlates”, “mechanism”, “factors”, and “association”. Articles were selected if they were in English language and to ensure a comprehensive review of the literature surrounding osteoarthritis fatigue, articles were included regardless of publication year. Articles were then reviewed and included if they measured fatigue in participants with osteoarthritis and examined its relationship with other variables. In addition, backwards reference searching was performed to identify additional research that included correlates of fatigue in osteoarthritis.

The conceptual framework we selected to discuss and synthesize the findings of this review was an adaptation of the Biobehavioral Model of Symptom Management from Ameringer and Smith (2011). In brief, the Biobehavioral Model of Symptom Management suggests that within the context of a health experience, there are personal factors, disease-related factors, and biological and behavioral moderators that interact with biological mediators to explain symptoms or symptom clusters affecting health outcomes (Ameringer and Smith, 2011). Our adaptation of this conceptual framework was titled the Biobehavioral Model of Fatigue in Osteoarthritis (Fig. 1). After presenting and discussing the identified correlates from the literature, we began to synthesize the findings within this framework. Thus, we grouped the correlates into Biobehavioral Factor categories including: individual factors (synonymous with personal factors), disease specific factors (synonymous with disease-related factors), behavioral factors, and biological factors similar to those found in the model proposed by Ameringer and Smith (2011), in addition to psychosocial factors (not part of the original model) which can be distinct from factors that fall within any of the other categories. Ultimately, the Biobehavioral Model of Symptom Management was adapted because of its parsimonious framework that is all inclusive of a large number of factors that likely contribute to a phenomenon.

Results

Table 1 presents an overview of the factors identified as known or potential correlates of osteoarthritis fatigue to be reviewed here.

Sex. A majority of osteoarthritis fatigue research demonstrates that women have higher levels of fatigue when compared to men (Botterman et al., 2016; Hawker et al., 2010, 2011; Jebakani et al., 2013; Wolfe et al., 1996). Over time, the odds of a high fatigue trajectory is 1.24 times higher for women compared to male (Botterman et al., 2016). In fact, the odds of low fatigue over time is more than two times higher for males compared to women (Botterman et al., 2016). However, previous findings suggests no difference in osteoarthritis fatigue by sex (Cross et al., 2008). Similar to the trend in the fatigue-age relationship, a vast majority of the research suggests female sex is positively associated with fatigue in osteoarthritis.

Age. While fatigue is a common complaint among older persons (Alexander et al., 2010), evidence to support a fatigue-age relationship in osteoarthritis is inconsistent. Multiple studies have found a relationship between age and osteoarthritis fatigue, but the direction of the relationship varies. Several studies show increased age is associated with increased osteoarthritis fatigue (Hawker et al., 2011; Stebbings et al., 2010). Yet one study found age was only positively associated with physical fatigue in osteoarthritis (Kratz et al., 2013). While another study showed that increased age is associated with decreased osteoarthritis fatigue (Castrejon et al., 2016). Nonetheless, the research suggests age is positively associated with fatigue in osteoarthritis.

Comorbidities. Several studies have begun to elucidate a relationship between comorbidities and osteoarthritis fatigue. Adults with comorbid conditions are 67% less likely to have a low fatigue trajectory over time when compared to an adult without a comorbid disease (Botterman et al., 2016). Specifically, a higher number of comorbid conditions is positively associated with worse fatigue (Zullig et al., 2015). Specific disease processes associated with worse osteoarthritis fatigue include depression and diabetes mellitus (Zullig et al., 2015). Moreover, when adults with knee or hip osteoarthritis report joint pain beyond their affected knee(s) or hip(s), they are more severely fatigued compared to those with localized pain (Hoogeboom et al., 2012). These findings suggest that having multiple diseases, in conjunction with an osteoarthritis diagnosis, results in higher levels of fatigue.

Medications. Drugs and drug side effects are known to contribute to fatigue in a variety of populations, especially among older adults. Several studies have shown that drugs commonly prescribed for osteoarthritis pain management are associated with fatigue including non-steroidal anti-inflammatory drugs (NSAIDs) (Botterman et al., 2016), sleep aids (Endeshaw, 2015), and analgesics like opioids (Turk and Cohen, 2010). Yet each type of medication likely has a different association with osteoarthritis fatigue. Adults with osteoarthritis report their prescribed medications, typically those taken for pain, contribute to their symptoms of fatigue (Power et al., 2008) and use of sleep-promoting medications is positively associated with fatigue (Turk and Cohen, 2010). Conversely, the odds of having a low fatigue trajectory was four times higher for NSAID users compared to adults not using NSAIDs when accounting for the effects of age, sex, comorbidities, and osteoarthritis severity (Botterman et al., 2016). These findings suggest that pain management through usage of NSAIDS, compared to other pain medications, may have a protective effect for osteoarthritis fatigue. No additional research was found to explore fatigue in osteoarthritis in relation to other classes of medications.

Disease Severity. Disease severity in osteoarthritis is typically determined via grading the amount of joint degeneration based on the Kellgran-Lawrence grading system using radiologic evidence. Using the Kellgran-Lawrence grading system, a radiograph of an affected joint is

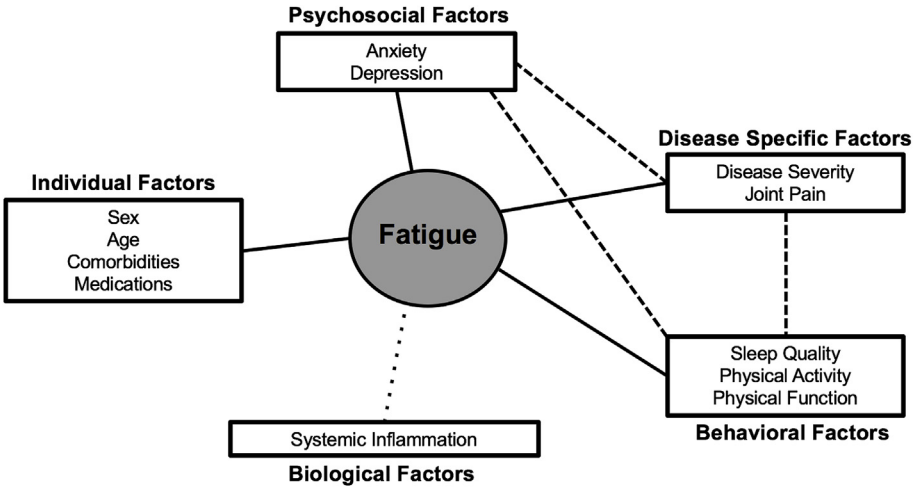

Fig. 1. Biobehavioral Model of Fatigue in Osteoarthritis.Adapted from Ameringer, S. & Smith, W. R. (2011). Emerging biobehavioral factors of fatigue in sickle cell disease. *J Nurs Scholarship, 43* (1), 22–29. Solid lines indicate established direct relationships with osteoarthritis fatigue; dashed lines indicate indirect relationships to osteoarthritis fatigue; and dotted lines indicate potential, not well-explored relationships in osteoarthritis fatigue.

Table 1
Correlates of fatigue in osteoarthritis.

Correlate	Biobehavioral Grouping
Sex	Individual Factor
Age	Individual Factor
Comorbidities	Individual Factor
Medications	Individual Factor
Disease Severity	Disease Specific Factor
Joint Pain	Disease Specific Factor
Depression	Psychosocial Factor
Anxiety	Psychosocial Factor
Sleep Quality	Behavioral Factor
Physical Activity (with Physical Exercise)	Behavioral Factor
Physical Function	Behavioral Factor
Systemic Inflammation	Biological Factor

assigned a grade from 0 to 4, which correlate with increasing severity of osteoarthritis (Grade 0 indicates no presence of osteoarthritis and Grade 4 indicates severe osteoarthritis) (Kohn et al., 2016). Several cross-sectional and longitudinal studies found a non-significant relationship between osteoarthritis severity and fatigue (Botterman et al., 2016; S.L. Murphy and Smith, 2010; Stebbings et al., 2010) and osteoarthritis severity was not a predictor of fatigue in unadjusted or adjusted regression models (Stebbings et al., 2010). Combined, this evidence does not support a relationship between radiological evidence of disease severity and osteoarthritis fatigue.

Joint Pain. A large amount of evidence highlights a positive relationship between joint pain and fatigue in osteoarthritis (in addition to physical and mental fatigue) (Castrejon et al., 2016; Huang et al., 2015; Murphy et al., 2016b; Murphy and Smith, 2010; Power et al., 2008; Smith and Parmelee, 2016; Wolfe et al., 1996; Zautra et al., 2007). Furthermore, adequate joint pain management through physical therapy or analgesic use is associated with decreased fatigue trajectory (Botterman et al., 2016; Snijders et al., 2011).

Two studies did not find a relationship between pain and osteoarthritis fatigue (Stebbings et al., 2010; Novaes et al., 2011), and, instead, highlight that other factors have a stronger, more significant relationship with osteoarthritis fatigue. For instance, Stebbings et al. (2010) found pain to be a significant predictor of osteoarthritis fatigue in an unadjusted linear regression model until age, inflammatory levels, disease severity, sleep quality, depression, anxiety, physical function, and disability were accounted for. Supporting this, Novaes et al. (2011) found osteoarthritis fatigue was more significantly associated with disability compared to pain. Nonetheless, the literature generally supports the notion that a positive relationship exists in some measure between joint pain and fatigue in osteoarthritis.

Depression. Several studies show a positive relationship between depression and fatigue in osteoarthritis (Carlesso et al., 2016; Castrejon et al., 2016; Power et al., 2008; Sale et al., 2008; Stebbings et al., 2010). Conversely, Zautra et al. (2007) demonstrated that when joint pain is accounted for, depression is no longer a significant contributor to osteoarthritis fatigue. This suggests that though osteoarthritis fatigue and depression have a positive association, joint pain may alter the relationship (Hawker et al., 2011).

Anxiety. Two recent studies provide mixed findings for the relationship between osteoarthritis fatigue and anxiety. One study reported increased osteoarthritis fatigue to be moderately correlated with higher anxiety (Carlesso et al., 2016), while another found osteoarthritis fatigue and anxiety were not significantly correlated (Castrejon et al., 2016). Collectively, the description of this relationship is inconclusive.

Sleep Quality. Adults with osteoarthritis often report poor sleep quality or sleep disturbances (Taylor-Gjevre et al., 2011), that is associated with significantly higher fatigue compared to adults with osteoarthritis reporting normal sleep (Castrejon et al., 2016; Hawker et al., 2010; Stebbings et al., 2010). Additional research showed that with short term improvements in overall sleep quality there are long term reductions in fatigue (Vitiello et al., 2014). Although there exists a fatigue-sleep quality relationship in osteoarthritis, prior research suggests poor sleep quality is associated with joint pain experienced during the night (Gignac et al., 2006), which may exacerbate fatigue during the day. When adjusting for the effect of pain, sleep quality no longer significantly contributes to osteoarthritis fatigue (Zautra et al., 2007). Thus, it is likely a fatigue-sleep quality relationship in osteoarthritis exists, but it is moderated by joint pain.

Physical Activity. Physical activity is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure” and includes physical exercise (Peeters et al., 2013, p. 661). Clinical practice guidelines in osteoarthritis recommend participation in physical activity and exercise for pain management and preservation of joint function (National Clinical Guideline Centre, 2014). However, osteoarthritis fatigue is a barrier for adults to participate in physical activity (Petursdottir et al., 2010) and may explain why those with osteoarthritis have lower average and peak physical activity over time (Murphy et al., 2008). For instance, women with hip or knee osteoarthritis exhibit decreased physical activity when feeling fatigue, a relationship consistent even when accounting for pain (Murphy et al., 2008). Adults with osteoarthritis are four times more likely to have increased fatigue after periods of high activity (Murphy et al., 2012). But adults with osteoarthritis who preplan activities and alternate between rest and activity have less activity associated fatigue (Murphy et al., 2012). With adequate preplanning and alternating rest with bouts of activity, adults with osteoarthritis may be able to mitigate fatigue

and increase physical activity. This works best when the alternation of activity and rest periods are individualized (based on an individual's specific relationship between activity and symptoms) (Murphy et al., 2010; Murphy and Kratz, 2014). Even though one study found tailored activity pacing had no effect on improving osteoarthritis fatigue (Murphy et al., 2016a), most findings suggest an underlying positive relationship between fatigue and physical activity in osteoarthritis.

Physical Exercise. Recent literature found that a variety of physical exercises significantly decrease osteoarthritis fatigue in the short and long term (Casilda-López et al., 2017; Park et al., 2017; Wyatt et al., 2014). Light exercises like walking, chair yoga, and Tai Chi stretching are effective in reducing osteoarthritis fatigue immediately post-intervention but had no long term effects on fatigue (Park et al., 2017; Wyatt et al., 2014; Yip et al., 2008). Conversely, moderate aerobic exercise such as a dance aquatic program (Casilda-López et al., 2017) or resistance training (Hennig et al., 2015) resulted in sustained reductions in osteoarthritis fatigue for three months. These outcomes support the notion that physical exercise is negatively associated with osteoarthritis fatigue in some fashion. More explicitly, only aerobic or resistance exercises were associated with improving osteoarthritis fatigue over the long term when compared to more gentle exercise (e.g., yoga, Tai Chi) or no exercise.

Physical Function. Physical function is defined as the ability to undertake everyday tasks (e.g., sitting, standing, walking) (Peeters et al., 2013). A large amount of research has explored the relationship between physical function and fatigue in older adults with osteoarthritis, finding that with increased fatigue there is an increase in functional impairment. Furthermore, when fatigue is improved there is a decrease in functional impairment (Carlesso et al., 2016; Liao and Ferrell, 2000; Parrish et al., 2008; Schepens et al., 2012; Snijders et al., 2011; Wolfe, 1999).

Some evidence suggests functional ability may also affect fatigue. Following performance of various physical function tasks (i.e., sweeping, reaching, lifting and carrying, and walking) fatigue initially increases and then there is a decrease in performance of additional tasks (Schepens et al., 2012). Further complicating the relationship between physical function and osteoarthritis fatigue, some research shows that functional ability mediates the relationship between fatigue and physical activity. With increased physical function there is a negative fatigue-physical activity relationship in osteoarthritis (Murphy et al., 2013). Despite this, there exists a close negative association between osteoarthritis fatigue and physical function.

Systemic Inflammation. Only one study explored the relationship between systemic inflammation and fatigue in osteoarthritis, and found higher blood c-reactive protein (CRP) levels had the strongest negative association with fatigue in osteoarthritis after adjusting for age, disease severity, sleep, pain, physical function, anxiety, and depression (Stebbings et al., 2010). However, the results were considered to be not clinically relevant because the mean level of CRP in the group was 4.2 mg/L and the lower limit of detection was 4 mg/L. Thus, the findings of this relationship are inconclusive. A more recent study conducted by Castrejon et al. (2016) explored inflammation in relation to symptoms of fatigue in osteoarthritis and found no significant association. However, inflammation was localized to affected joints as opposed to systemic and was measured by a physician using a highly subjective subscale from the RheuMetric. Thus, there is a lack of evidence to characterize the relationship between fatigue and systemic inflammation in osteoarthritis.

Biobehavioral Model of Fatigue in Osteoarthritis

Our adapted Biobehavioral Model of Fatigue in Osteoarthritis (Table 1) synthesizes the findings reviewed here and proposes that in osteoarthritis, individual, disease specific (specific to the disease process of osteoarthritis), psychosocial, behavioral, and biological factors are related to fatigue. Potential individual factors reviewed as correlates to osteoarthritis fatigue include age, sex, medications, and comorbidities; disease specific factors include disease severity and joint pain; psychosocial factors include depression and anxiety; behavioral factors include sleep quality, physical activity (which may include exercise), and physical function; and biological factors include systemic inflammation.

This evidence was used to design Fig. 1. The model highlights the relationships discussed here. Direct relationships between factors of the Biobehavioral Model and osteoarthritis fatigue as depicted as solid lines, indirect relationships between some factors to influence osteoarthritis fatigue are depicted as dashed lines (e.g., joint pain and sleep quality), and dotted lines indicate the potential, not well-explored relationships (e.g., systemic inflammation). In order to not indicate direction, because the literature research is in its infancy, lines were used to imply a relationship between the factors.

Discussion

Although osteoarthritis fatigue is less well researched compared to fatigue in other diseases, the large amount of evidence reviewed here implies its significance and presents its potential correlates. It is important to note that this review does not claim causality among variables, but instead recognizes relationships. While the relations discussed vary, overall, there is a positive relationship between osteoarthritis fatigue and female sex, age, number of comorbidities, non-NSAID pain medication usage, joint pain, depression, poor sleep quality, general physical activity, decreased physical exercise, and impaired physical function. A handful of studies suggest no relationship between osteoarthritis fatigue and disease severity. Moreover, results about the relationship between osteoarthritis fatigue and anxiety or systemic inflammation were inconclusive. Collectively, these correlates can be synthesized within the Biobehavioral Model of Fatigue in Osteoarthritis, a model that can be used as a guide for discovery of mechanistic pathways underlying fatigue in osteoarthritis in future work.

It is important to address that while there was mixed or inconclusive evidence of the osteoarthritis fatigue relationship with anxiety, disease severity or systemic inflammation, additional research should incorporate these variables to further explore their relevance to osteoarthritis fatigue. It is possible that inclusion of these variables may show different and more consistent results in future studies. For instance, because systemic inflammation is related to symptoms of fatigue in other chronic diseases (Lakhan et al., 2009; Lasselin et al., 2012; Morris et al., 2015; Moss et al., 1999; Wood et al., 2006), and osteoarthritis is known to be inflammatory in nature (Hosnijeh et al., 2016; Pearle et al., 2007; Robinson et al., 2016; Sohn et al., 2012; Stürmer et al., 2004), it is logical to infer that there may be a significant relationship amongst these variables in osteoarthritis that is worth exploring. Thus, systemic inflammation, along with anxiety and disease severity have been retained in the Biobehavioral Model of Fatigue in Osteoarthritis.

As future research utilizes the Biobehavioral Model of Fatigue in Osteoarthritis for guiding study design, it is also important to consider that several studies discussed here found conflicting results amongst relationships between correlates and fatigue. This was true of the independent relationships between sex, age, joint pain, physical activity, and osteoarthritis fatigue. We believe these differences are likely related to variation in fatigue measurement and/or sample characteristics across studies. For instance, research reporting no differences in osteoarthritis fatigue by sex operationalized fatigue as a score of greater than three on the Fatigue Severity Scale (Cross et al., 2008). Whereas research confirming a fatigue-female sex relationship in osteoarthritis used more multidimensional instruments for measuring fatigue. Equally important to consider is that research confirming the osteoarthritis fatigue-female sex relationship had samples that were disproportionally female, with 65–89% of participants being female, thus males may have

been underrepresented.

Likewise, studies finding a positive relationship between fatigue and age in osteoarthritis had two commonalities: 1) participants had hip or knee osteoarthritis, and 2) comprehensive measures that explored dimensions of fatigue [e.g., Multidimensional Fatigue Inventory (MFI) or Multidimensional Assessment of Fatigue – Global Fatigue Index (MAF-GFI)] were used. Conversely, the single study supporting a negative fatigue-age relationship included participants with all types of osteoarthritis (Castrejon et al., 2016) and used a visual analog scale to measure fatigue. Further supporting this, research suggesting a positive association between fatigue and joint pain in osteoarthritis used visual analog or numerical rating scales to measure fatigue, while research that found no relationship used the MAF-GFI to measure fatigue (Novaes et al., 2011; Stebbings et al., 2010). Influences of sample characteristics may also exist in evidence that suggests tailored or individualized physical activity had no association with osteoarthritis fatigue. These studies included participants who had a low symptom burden, and the authors noted that people who were ineligible for the study typically exhibited higher levels of fatigue.

Ultimately the differences in outcomes in these few studies collectively emphasize the influence of sample characteristics and the importance of consistent measurement of fatigue across research. There is reason to believe these differences may also explain inconclusive findings. For example, studies finding a positive relationship between fatigue and anxiety (Carlesso et al., 2016) had participants with more significant joint impairments than participants in the study that found no fatigue-anxiety relationship (Castrejon et al., 2016). Moreover, the studies exploring disease severity included participants with knee or hip osteoarthritis and used multi-item instruments like the MAF-GFI (Stebbings et al., 2010). These findings further suggest that sample characteristics and variation in fatigue measurement may greatly influence what variables are correlates with osteoarthritis and how the relationship is defined. Therefore, it is important for future researchers to mindfully consider sample characteristics and fatigue measurement when exploring osteoarthritis fatigue and its correlates. Future research should strive for a sex-matched sample, account for osteoarthritis type, and consider the use of a standardized measure of fatigue so results are consistent and easily comparable across studies.

Nonetheless, while all of the relationships presented here require additional research, this review also highlighted several direct and indirect relationships to osteoarthritis fatigue that have not been studied. For example, the evidence of the association between medications and osteoarthritis fatigue focused on the side effect of fatigue as a result of the use of non-NSAID pain medications. Yet it is possible that other drug classes commonly prescribed to older adults may have similar effects on fatigue (e.g., anti-hypertensives, anti-diuretics, statins) but requires additional research. In addition, polypharmacy is a growing issue in older adults and is known to be associated with negative clinical consequences (Maher et al., 2014), which may include presence or exacerbation of fatigue in adults with osteoarthritis. Additionally, the fatigue-sleep quality relationship was consistent across studies, yet findings alluded to the notion that one way to manage poor sleep quality, as a way to alleviate osteoarthritis fatigue, may be through adequate pain control. Similar indirect relationships are presented in the evidence of the ability of pain and impaired physical function to impact the osteoarthritis fatigue-depression relationship (Hawker et al., 2011) or how functional ability may mediate physical activity and fatigue (Murphy et al., 2013). All of these provide unique directions for future work when exploring osteoarthritis fatigue.

It is also plausible that because our review was comprehensive but not exhaustive, other factors not discussed here are directly and indirectly associated with osteoarthritis fatigue. Examples of factors that may directly be related to osteoarthritis fatigue may include ethnicity and race, illness beliefs or patient perspectives, nutritional status, genetics, or environmental exposures, all not well studied in osteoarthritis fatigue. It is also possible that inclusion of additional factors in osteoarthritis research will highlight more indirect relationships that influence fatigue. For instance, relationships between systemic inflammation (biological factor) and age, medications (individual factors) (Franceschi and Campisi, 2014; Xiao et al., 2016), or physical activity (behavioral factor) (Ford, 2002; Woods et al., 2012) exist in other research, and may also exist in osteoarthritis fatigue. Although these are just some examples, all of the findings reviewed here provide insight into areas of needed research and guide future work toward mechanistic insight into osteoarthritis fatigue.

Conclusion

With the increase in the prevalence of osteoarthritis in the aging population, there will also be an increase of its associated symptomatology, including fatigue. The lack of knowledge regarding the etiology of fatigue in osteoarthritis is concerning. Currently, limited treatment options exist and untreated fatigue continues to contribute to functional limitations, decreased social engagement, and diminished quality of life. Here we have presented the current evidence of known and potential factors associated with osteoarthritis fatigue and synthesized our findings within a multifaceted model. While a systematic review may have been more rigorous and provided an overview of the methodological quality of the research discussed, there is only a small body of osteoarthritis fatigue research that conclusions could be based on. Therefore, a narrative literature review was an important first step toward encouraging work in this area.

Even with acknowledgement of this shortcoming, this is the first review to our knowledge that begins to outline and synthesize the correlates of fatigue in osteoarthritis. Such a synthesis of knowledge will be pivotal for future work in this area, as we have reviewed correlates of osteoarthritis fatigue and synthesized them into a multidimensional framework for future study design. Our discussion provides several areas in osteoarthritis fatigue research where this framework can be implemented. Our multidimensional framework, The Biobehavioral Model of Fatigue in Osteoarthritis (Fig. 1), will facilitate a multifaceted approach in examining the direct relationships and interplay between individual, disease specific, behavioral, psychosocial, and biological factors, and osteoarthritis fatigue. Research that incorporates such an approach is likely to produce findings that enrich the state of the science toward intervention design and testing by elucidating modifiable and non-modifiable pathways of osteoarthritis fatigue development. Only after such research is conducted can implications for clinicians and patients be conferred. Ultimately, this knowledge will increase our understanding of osteoarthritis fatigues' etiology, leading to novel nursing interventions for prevention, management, and treatment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijotn.2019.01.003.

Ethical statement

I testify on behalf of all co-authors that our article, *A review and synthesis of correlates of fatigue in osteoarthritis*, submitted to International Journal of Orthopaedic and Trauma Nursing:

1) Has not been published in whole or in part elsewhere;
2) Is not currently being considered for publication in another journal;

3) And all authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

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