REVIEW

Musculoskeletal fatigue in cancer patients with Cachexia: A systematic review

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ABSTRACT

Background: Cachexia is a multifactorial syndrome commonly seen in cancer patients, marked by significant weight and muscle loss, and is strongly associated with cancer-related fatigue (CRF). This condition results from an imbalance in muscle protein homeostasis, exacerbated by systemic inflammation and metabolic dysregulation. Understanding the relationship between muscle wasting and fatigue in cachexia can provide insights into potential therapeutic interventions.

Methods: A systematic review was conducted using databases such as PubMed, ScienceDirect, and EMBASE. Keywords included "cachexia," "cancer," "biomarker," and "fatigue." Inclusion criteria were studies involving cancer patients with cachexia, with fatigue as a primary outcome and musculoskeletal system biomarkers as key variables. After screening 3,434 articles, two studies met the inclusion criteria.

Results: Both studies emphasized the critical role of muscle mass and strength in fatigue. The first study demonstrated significant negative correlations between handgrip strength (HGS), quadriceps strength (QS), skeletal muscle mass index (SMMI), and fatigue levels (measured by the Brief Fatigue Inventory, BFI) in male patients, suggesting muscle wasting as a primary contributor to fatigue. The second study (n=83) found no significant associations between fatigue and inflammatory cytokines such as IL-1b, IL-6, IL-8, and TNF-α, challenging the conventional view of inflammation as the primary driver of fatigue in cachexia.

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Discussion: The findings highlight muscle bioenergetic inefficiency and metabolic disorders as key mechanisms underlying fatigue in cancer cachexia, with inflammatory pathways playing a less significant role. Gender differences in musculoskeletal markers' influence on fatigue underscore the need for tailored interventions.
Conclusion: Muscle wasting is a central determinant of fatigue in cancer cachexia, while the role of inflammation remains inconclusive. Further research is essential to explore alternative mechanisms and develop targeted therapies.

Key words: cancer, cachexia, musculoskeletal fatigue

Introduction

Cancer is the second leading cause of death in the world after cardiovascular disease, with an estimated 19.3 million new cases and nearly 10 million deaths by 2020 (1,2). In cancer patients, cachectic syndrome often presents as a complex and multifactorial condition, characterized by a weight loss of more than five percent in the last six months in the absence of a starvation phase. Cachexia can also be recognized through a body mass index (BMI) below 20 with a weight loss of more than two percent or through a low appendicular skeletal muscle index. This syndrome not only occurs in cancer, but also in other chronic diseases such as heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis(3). Cancer patients with cachexia often show severe symptoms of cancer-induced fatigue, which is one of the main symptoms that have an impact on reducing quality of life(4). Fatigue in cachexia patients is closely related to the phenomenon of muscle wasting, which is a decrease in muscle mass and strength caused by an imbalance in the process of protein and myonuclear turnover in muscle (5). Under normal conditions, muscle protein synthesis and degradation are in homeostatic balance. However, in cachexia, this process is disrupted, leading to decreased muscle protein synthesis and increased muscle protein degradation, as well as inhibition of myonuclear growth, all of which accelerate muscle wasting (6). Muscle wasting leads to reduced mobility in patients and triggers fatigue as muscles become less efficient (7). Research shows that the musculoskeletal system, specifically muscle mass and strength, has a significant influence on fatigue in cachectic patients. Kilgour et al (8) found that cancer can trigger the release of proinflammatory cytokines such as TNF-α, IL-6, IL-1, and interferon-γ, which not only stimulates muscle degradation but also triggers fatigue in patients (7,9). In the acute phase, these cytokines are necessary to enhance the immune response against tumors, but in chronic inflammation, their production exacerbates cachexia and accelerates muscle wasting (10). Cytokines such as TNF-α and IL-6 act at multiple levels to disrupt protein homeostasis, increase protein degradation through the proteasome system, and inhibit protein synthesis in muscle (6). In addition, IL-6 and TNF-α are known to inhibit erythropoesis, which contributes to fatigue (9). In addition to inflammation, inadequate nutritional intake may also exacerbate muscle wasting in cancer patients. However, according to Kilgour et al, (8) the impact of this nutritional deficiency is not as strong as the direct effect caused by increased proinflammatory cytokines on muscle wasting (11,12). This indicates that although nutrition is important, the musculoskeletal and inflammatory systems have a greater role in determining fatigue in patients with cachexia. Nutrition is more a supportive factor in patient management to improve quality of life, rather than the primary factor influencing fatigue due to cachexia.

Given the large role that muscle wasting and proinflammatory cytokines play in fatigue symptoms in cancer patients with caesarea, it is important to understand the relationship between these components of the musculoskeletal system and fatigue symptoms. This literature review aims to summarize the findings

of studies that have been conducted on the role of the musculoskeletal system on fatigue symptoms in cancer patients with cachexia, particularly through muscle wasting.

Methods

This research is a type of qualitative research that is a literature study. Literature study can be defined as a series of activities related to library data collection methods, reading, and recording and processing materials, which come from various sources such as the internet, journals and books. Overall, this research is included in a literature study using the literature review method. The research uses data from results of studies that have been conducted and published on the PubMed, Science Direct, EMBASE, Oxford Journal, Springer, ProQuest, Sage Journal, Scopus, and EBSCOhost databases. The keywords to be used are ("cachexia" OR "wasting syndrome") AND "cancer" AND ("biomarker" OR "test") AND ("fatigue"). This study uses data from research results that have been published in online journals, both national and international. The collected articles were then selected on the basis of predetermined inclusion and exclusion criteria. The selection process was independently performed by three reviewers: TFS, a master's student in biomedical sciences with a focus on anatomy; MRAS, a physician holding a PhD in biochemistry; and IR, a physical medicine and rehabilitation specialist with a PhD. Any disagreements during the selection phase were resolved through discussion to reach a consensus. The inclusion criteria in the journal collection included: the study population was composed of patients with cancer who had been diagnosed by a doctor, the intervention tested was the effect of musculoskeletal system biomarkers on fatigue symptoms in patients, the study had the main outcome in the form of fatigue symptoms, and the type of study included was original research (original article). Exclusion criteria included unavailability of full versions of research articles and studies written in languages other than Indonesian or English. The literature review began with the collection of articles that met the inclusion with relevance defined by the inclusion of cachectic cancer patients, fatigue as a primary outcome, and analysis of musculoskeletal biomarkers. The abstracts of the articles were read carefully to assess the relevance of the data to the study to be reviewed. Key points from the research were noted and adapted to the review. To avoid plagiarism, sentences were rearranged through the process of paraphrasing, noting the sources of information, and listing them in the bibliography. Next, the studies that met the inclusion criteria were analyzed, and the results of the analysis were compiled into a literature review. In the process of preparing this literature review, the instruments used included laptop devices, the internet, search applications such as PubMed, ScienceDirect, and EMBASE, and data processing applications such as Mendeley and Microsoft Word.

Results

In our comprehensive systematic search process, we managed to collect 3434 studies from various databases. The results of this search were then broken down in stages, as visualized in the flowchart presented in Figure 1.

A literature search was conducted using several databases, namely PubMed, ScienceDirect, EMBASE, Oxford Journal, Springer, ProQuest, Sage Journal, Scopus, and EBSCOhost. The search aimed to identify relevant studies on cancer patient dysphoria and its biomarkers, with a particular focus on fatigue as one of the key indicators. The search terms used were a combination of several keywords, namely: ("cachexia" OR "wasting syndrome") AND "cancer" AND ("biomarker" OR "test") AND ("fatigue"). At the initial stage, 3,434 articles were found from various databases. After the duplication removal process, 1,555 unique articles were obtained for the filtering stage. Each article was then screened by title and abstract to exclude irrelevant studies, leaving 20 articles for further review in full text. In this context, "irrelevant" refers to studies that did not meet the inclusion criteria in terms of (1) outcomes—i.e., studies that did not investigate fatigue or only mentioned it incidentally; (2) study design—such as editorials, reviews, or conference abstracts without full data; (3) population—studies involving non-cancer patients

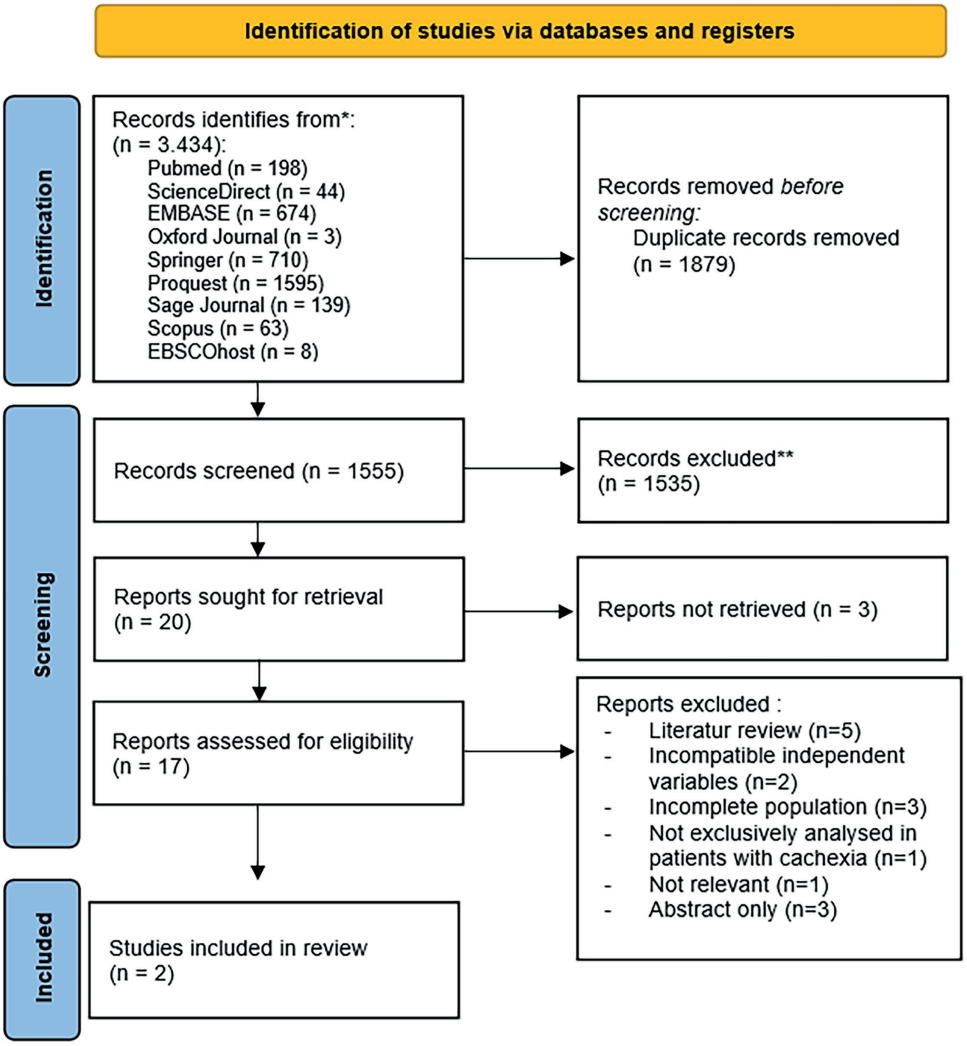

Figure 1. PRISMA flowchart diagram

or cancer patients without cachexia; and (4) independent variables—studies that did not assess musculoskeletal biomarkers or related physiological parameters. From this review, 17 studies were excluded based on certain criteria, namely literature review (n = 5), incompatible independent variables (n = 2), incompatible populations (n = 3), not exclusively examining patients with cachexia (n = 1), irrelevant based on outcome indicators (n = 1), and abstract only (n = 3). The final literature search was conducted on April 20, 2024. After a rigorous selection process, two studies (8,13) were judged to meet our inclusion criteria. Most studies were excluded because the fatigue parameters used were not relevant to the musculoskeletal system or because the study subjects were not cancer patients diagnosed with cachexia. The included studies are detailed in Table 1. In a cross-sectional study conducted by Kilgour et al(8) 84 subjects were studied, with a mean age of 61.6 ± 13.2 and a mean BMI of 24.1 ± 5.4. The study population was roughly balanced between genders with 48 males and 36 females. The type of cancer documented was predominantly gastrointestinal (GI) with 68 cases, followed by non-small cell lung cancer (NSCLC) with 16 cases. Cancer stage was divided between locally advanced (36 cases) and metastatic (48 cases). In particular, several muscle parameters

Table 1. Summary of study characteristics

Design	Sample number	Age	BMI	Ratio M/F	Types of Cancer	Cancer Stadium	Results	Quality
Kilgour et al. (2010), cross-sectional	84	61.6 ± 13.2	24.1 ± 5.4	48/36	NSCLC = 16; GI cancer = 68	Locally advanced 36; Metastatic 48	**Bivariate Linear Regression:** *Arm lean mass* B = −0.004*** (CI 95% −0.007 to −0.001) *Leg lean mass* B = −0.001*** (CI 95% −0.003 to −0.001) SMMI (kg/m^2) B = −4.8** (CI 95% −8.4 to −1.3) HGS B = −0.6*** (CI 95% −1.1 to −0.15) QS B = −0.1*** (CI 95% −0.2 to −0.01) HGS *muscle quality* B = −0.6 (CI 95% −2.6 to 1.4) QS muscle quality B = −1.2 (CI 95% −2.5 to 0.03) **Correlation:** HGS (r = −0.34; p = 0.018), QS (r = −0.39; p = 0.024) and SMMI (r = −0.60; p < 0.001) negatively correlated with BFI total score in men but not in women **Multivariate Linear Regression:** BFI scores were negatively associated with HGS (B = -0.90; CI 95% -1.5:-0.3), QS (-0.2; CI 95% -0.3:-0.01), and SMMI (-7.5; CI 95% -13.0:-2.0). There was a significant sex × SMMI interaction (10.8; 1.2:20.5), where BFI decreased with increasing SMMI in men, but did not change with increasing SMMI in women.	Good Quality
Scheede-Bergdah et al. (2011), cross-sectional	83	61.8 ± 12.9 (34-85)	24.1 ± 5.4	47/36	NSCLC = 14; GI cancer = 69	Locally advanced 34; Metastatic 49	None of the cytokine showed an association with fatigue based on BFI. IL-1b -> B = 8.80 (CI 95% −4.57; 22.17) IL-6 -> B = 10.78 (CI 95% −2.67; 24.24) IL-8 -> B = 5.37 (CI 95% −7.72; 18.46) TNF-a -> B = 4.60 (CI 95% −8.93; 18.13)	Good Quality

**p<0.01; ***p<0.05. *Abbreviations:* M: male; F: female; BMI: body mass index NSCLC: non small cell lung cancer; GI: gastrointestinal cancer BFI: brief fatigue inventory;; HGS: handgrip strength; QS: quadriceps strength; SMMI: skeletal muscle mass index.

were significantly associated with the measured outcomes. For example, arm lean mass, leg lean mass, SMMI (skeletal muscle mass index), handgrip strength (HGS), and quadriceps strength (QS) all showed significant negative regression coefficients. Furthermore, HGS, QS, and SMMI had negative correlations with the brief fatigue inventory (BFI) total score in men, but not in women. In addition, multivariate regression analysis showed that BFI scores were negatively associated with HGS, QS, and SMMI. This study was judged to be of good quality based on National Institsute of Health Quality Assessment tool (8,13). In another cross-sectional study by Scheede-Bergdah et al.(13) a total of 83 subjects were evaluated. They had a mean age of 61.8 ± 12.9 years, ranging from 34 to 85 years, and a mean BMI of 24.1 ± 5.4. The gender distribution was 47 males and 36 females. The majority of participants had gastrointestinal cancer (69 cases), followed by non small cell lung cancer (NSCLC) (14 cases). The cancer stages found were locally advanced (34 cases) and metastatic (49 cases). This study focused on the relationship between fatigue and various cytokines. The results showed that none of the cytokines, including IL-1b, IL-6, IL-8, and TNF-a, showed a significant association with fatigue based on the BFI score. This study was also rated as good quality based on National Institsute of Health Quality Assessment tool (13).

Discussion

In the two studies that we managed to find, there were some similarities, namely the number of subjects amounted to a range of 83 patients, the average age was 61 years, the body mass index was 24 kg/m2, the ratio of men and women was 47-48: 36, and the cancer types were NSCLC and Gastro-Intestinal Cancer. The first study by Kilgour et al (8) emphasized the significant negative correlation between BFI and HGS, QS, and SMMI scores in men diagnosed with cancer and cachexia. This is in accordance with another comprehensive systematic review and meta-analysis, which extensively explored the relationship between muscle strength, body composition and CRF in cancer patients in general (8). This review highlighted HGS as a repeatable parameter to measure the relationship between muscle strength and CRF. The repeated use of HGS across studies underscores the importance of HGS as an effective metric. The mean range of HGS across these studies oscillated between 18.5 to 32.7 kg among cancer patients. Although most of these studies showed a negative association between HGS and CRF, some studies showed no correlation, suggesting a more complicated relationship (8). The decrease in muscle mass, characteristic of cachexia, can be framed in terms of muscle bioenergy theory. Reduced muscle mass may impact the cellular energy system, leading to fatigue. Muscle cells, with decreased structural integrity, may become inefficient in the production of ATP, the key molecule responsible for energy in cells (14). This reduction may help explain why patients with cancerous cachexia experience increasingly severe fatigue. In addition, the relationship between muscle strength and CRF may be mediated by inflammatory cytokines, which are elevated in cancer and cachexia. These cytokines may affect neural activity, potentially leading to a subjective sense of fatigue (15). HGS, as a measure, may indirectly reflect the body's inflammatory state, with lower HGS signaling higher levels of inflammation. Delving into sociocultural theories may explain the gender differences found in our study. Societal perceptions and expectations of strength, especially in men, may play a role in how men perceive and report their fatigue levels. The loss of perceived 'masculine strength' may exacerbate the psychological impact of muscle loss, leading to higher fatigue (8). The study conducted by Scheede-Bergdah et al (13) is particularly noteworthy as it explores the relationship between cancer-related fatigue and specific cytokine levels (13). Although existing literature highlights a strong association between fatigue and circulating inflammatory cytokines, the findings from this study provide a contrasting perspective (13). Specifically, this cross-sectional study found no significant correlation between fatigue in cancer patients with cachexia, as measured by the BFI score, and the cytokines IL-1b, IL-6, IL-8, and TNF-a (13). The complex interactions between inflammation, metabolic byproducts and fatigue have been the concern of many researchers. Fatigue rise due to the accumulation of metabolic byproducts such as lactate in muscles, compounded by the depletion of metabolic fuels, especially glucose. The liver

plays a central role in managing these metabolic processes (16,17). During phases that require energy or food lack, the liver actively maintains blood glucose levels by utilizing stored glycogen or producing glucose from precursors such as amino acids and lactate through processes such as the Cahill and Cori cycles (18). This is not only important for maintaining glucose levels but also preventing lactate-induced acidosis in the muscles. In addition, the liver is the epicenter of the inflammatory response, releasing critical proteins and cytokines-a very energy-draining process. In the context of cancer, the inflammatory response triggered in the liver can magnify the metabolic impact of the tumor. At the same time, it can also challenge the liver's ability to maintain a consistent metabolic environment (16). Findings from the study by Scheede-Bergdah et al (13) introduce an interesting contribute to our understanding of the mechanisms underlying cancer-related fatigue in patients with cachexia. Cachexia, characterized by severe muscle shrinkage and weight loss, is commonly seen in many cancer patients. The unexpected lack of association between fatigue and cytokines in this particular group prompted a deeper exploration of the unique physiologic changes that occur in cancer patients with cachexia (13). One hypothesis is that the metabolic disorders seen in cachexia may overshadow or modulate the typical inflammatory pathways associated with fatigue (13). Cachexia results in profound changes in energy metabolism, with increased breakdown of muscle protein and fat (13). This altered metabolic state may lead to different fatigue mechanisms, where the primary driver is not necessarily the inflammation but the metabolic imbalance itself (13). Thus, traditional inflammatory markers, including IL-1b, IL-6, IL-8, and TNF-a, they not show the same correlation with fatigue in the cachexia state as they do in cancer patients without cachexia (13) Another consideration is the multifactorial nature of fatigue. Beyond inflammatory and metabolic factors, fatigue can be influenced by several other factors, including psychological distress, sleep disturbances, and medication side effects, among others (19). For patients with cachexiasevere weight loss and muscle loss can increase the perception of fatigue, regardless of inflammatory markers. Therefore, the role of cytokines may be less clear or overshadowed by other factors that predominate in these patients. In addition, the potential influence of the tumor itself, which releases factors that contribute to muscle damage and potentially fatigue, may be another area of investigation (19).

Conclusion

This systematic review revealed a consistent negative correlation between musculoskeletal system condition and fatigue levels in male cancer patients diagnosed with cachexia. In particular, HGS, QS, and SMMI emerged as the main predictors of fatigue. However, the relationship between fatigue and commonly associated inflammatory cytokines appeared ambiguous in cachexia patients, suggesting the existence of alternative physiological mechanisms. Considering the limited literature sources to review, institutional support is needed to encourage experimental research on the role of the musculoskeletal system on fatigue symptoms in cancer patients with cachexia.

Authors' Contribution: All authors contributed substantially to the manuscript. TFS was responsible for conceptualization, methodology, validation, investigation, data care, writing of original draft, and project administration. Both MRAS and IRD contributed equally in review and editing of original draft as well as supervision.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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