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Effectiveness of supervised physical therapy exercise in the management of cancer-related fatigue: A Systematic Literature Review (SLR)

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Abstract

Cancer-related fatigue (CRF) is a common and debilitating condition seen in patients during and after cancer treatment. Despite advances in the understanding or risk factors and mechanisms of CRS, it is notable that CRS symptoms and poor treatment outcomes are underreported. Although it remains unclear whether supervised strategies, led by physiotherapists and associated healthcare professionals, are necessary to achieve optimal results. The aim of this structured literature review was to assess the benefits of supervised exercise-based interventions in adult patients with Cancer-Related Fatigue (CRF). A structured literature review was completed to meet the defined aim, using online journal databases. Studies comparing active exercise interventions, supervised by physiotherapists, with active or control groups were considered, with a publication range of 2010-2020. The most important findings were that the short-term benefits of active exercise outweighed the control groups and psychological interventions, while the supervised exercise appeared to have benefits over the unsupervised exercise. It indicates that supervised exercise interventions can have beneficial effects on fatigue in CRF patients. Careful consideration of the data set is needed to take into account heterogeneity in the patient population, approved interventions, and the outcomes evaluated.

Key words: **Cancer, Physical therapy, Fatigue, CRF.**

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1 Introduction

Cancer refers to a broad category of diseases in which cells suffer from uncontrolled growth with the potential to become malignant due to persistent angiogenesis, immune evasion, and other disturbed features (Umm, 2015). It is estimated that globally more than 10 million people have been diagnosed with some form of cancer, while another 25 million people have survived cancer (Jones & Grunfeld, 2011). Cancers are a major cause of mortality worldwide, contributing to morbidity and poor quality of life in affected individuals (Elmore et al., 2020). Cancer diagnosis rates are increasing and there will be at least 1.7 million new diagnoses in 2020 alone (Jones & Grunfeld, 2011; Bower, 2014). These trends reflect improved diagnoses and early detection of many cancers, as well as increases in the prevalence of certain types of cancer, including breast, lung, prostate and bowel cancer (World Health Organization [WHO], 2018). Therefore, the expected burden of care related to cancer is expected to rise significantly over time.

One challenge in cancer care is that many of the initial symptoms of cancer are nonspecific in nature, including fatigue, weight loss, and malaise (Escalante et al., 2010). Symptoms may prevent early diagnosis in many patients until the cancer has reached a size sufficient to form a palpable mass or affects the local anatomy (Ingeman et al., 2015). The effects of cancer growth vary according to the location of the tumor and histopathological characteristics of the tumor, producing specific presentations depending on the type of cancer (Ingeman et al., 2015). However, malignant carcinomas collectively constitute an important class of carcinomas with similar clinical characteristics and outcomes. Moreover, many cancers, especially in the early stages but also in the later stages, can be controlled with radiotherapy, chemotherapy or surgery, which are associated with variable rates of therapeutic response, as well as specific side effects such as fatigue, delirium and anorexia (Baetke et al., 2015). It is clear that both the condition and the treatments used to manage cancer can have many negative effects on an individual's health status (WHO, 2018).

Numerous CRF papers suggest that risk factors and specific mechanisms may be of great importance in the context of cancer (Bauer, 2014). The greatest level of experimental support for cellular dysregulation has been observed as a major cause of CRF (Bower, 2014). Cytokines are an important group of signaling molecules that play a key role in regulating immune responses, especially inflammatory reactions (Bower & Lamkin, 2013). Cytokines can be released in response to a pathogen within the body, as inflammatory reactions promote effective immune filtering of pathogens. However, under pathological conditions, cellular expression can lead to widespread inflammation at the systemic level (Eyob et al., 2016). Inflammation may lead to a range of tissue dysfunctions and negative effects on cellular processes, resulting in chronic disease states or the potential for fatigue (Fung et al., 2013).

Although knowledge of the causes and consequences of CRF has expanded over time, many challenges in the treatment and management of CRF remain to be addressed in a clinical setting. There is a significant gap in the literature regarding the efficacy of exercise-based treatments for CRF, particularly in terms of applicability of different interventions and optimal intervention design for different patients. The aim of the search in this structured review of the literature was therefore to evaluate the benefits of supervised exercise-based interventions in adult patients with cancer-related fatigue (CRF).

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2 Literature review

2.1 Cancer-related fatigue

CRF is one of the most common phenomena in people with cancer (Berger et al., 2015). The onset of fatigue may coincide with the initial malignant disease process, the establishment of a cure for the disease, or during recovery from cancer (Bower, 2014). Although the CRF is recognized as being inherently common, estimates of prevalence vary widely (25–99%) due to differences in number of patients, type of cancer, type of treatment, and assessment methods used in the literature (Berger et al, 2010; Bauer, 2014) . It has been observed that about 30-60% of patients experience moderate to severe stress during cancer treatment (Bauer, 2014). While CRF may improve after cancer treatment, up to a third of cancer survivors may experience persistent fatigue for up to 10 years after initial diagnosis, suggesting that chronic fatigue is an important aspect of the long-term experience (Berger et al., 2007), 2015). The impact of a CRF on an individual can be very negative, affecting many aspects of quality of life and well-being (van der Lee & Garssen, 2012). Fatigue may be associated with a risk of low mood and depression in both cancer patients and cancer survivors (Borneman et al., 2012; Bower, 2014). It is important to note that depression is associated with chronic disease states and cancer may be associated with fatigue, which may complicate this relationship (Mustian et al., 2012). CRF may also have an impact on social and emotional well-being, stressing relationships and affecting family dynamics (Mustian et al., 2012).

The mechanisms associated with CRF appear to be largely related to neuronal/neuroendocrine signaling and/or inflammatory mechanisms (Bower, 2014). Interventions based on assessing the effects of neural mechanisms include psychosocial support mechanisms, which may improve negative coping strategies while promoting cognitive changes associated with neurotransmitter imbalance. In contrast, exercise-based strategies may effectively enhance positive psychological effects, reduce inflammation, or modulate other aspects of fatigue-related metabolism (Bower, 2014). Evidence in patients with CRF suggests that inflammatory markers may increase in response to the pathological process of cancer growth and spread, as well as in response to cancer treatment (Eyob et al., 2016). Key markers, including interleukins and C-reactive protein (CRP), have been identified at higher levels in patients undergoing chemotherapy and radiotherapy for cancer, and have been linked to the onset of fatigue associated with these treatments (Pertl et al., 2013). While it may be argued that an increase in inflammatory markers in this context may be a consequence of cancer treatment and, moreover, may not lead to outcomes such as fatigue, evidence suggests that dysfunction in inflammatory cytokine pathways may be chronically related onset of fatigue after treatment in patients with cancer (Saligan et al., 2015).

2.2 Mechanisms related to CRF and Treatment approaches to CRF

The mechanisms underlying the CRF may be controversial in nature, but the main findings and risk factors in the empirical literature suggest the usefulness of interventions aimed at promoting physical activity, psychosocial well-being, or modulating neuroendocrine signaling (Thong et al., 2020). Psychological approaches and the modulation of neuroendocrine signaling may have overlapping properties in the therapeutic context; including the use of psychological therapies and social strategies to enhance coping mechanisms and coping with cancer-related stress and/or fatigue (Bower, 2019). The use of psychological therapies, including psychotherapy and cognitive behavioral therapy (CBT), for depression and other conditions associated with debilitating fatigue justifies this strategy to some extent in CRF (Charalambous et al., 2019). Moreover, these therapies aim to address aspects of negative thought processes that can influence behaviors, and instill coping strategies to overcome fatigue at the cognitive level (Wu et al., 2019). Physical activity therapies, in contrast to psychological therapies, appear to target a wide range of pathways related to cognitive mechanisms and physiological processes (Thong et al., 2020). As with psychosocial interventions, physical activity interventions have been associated with broad improvements in mood, as well as well-being in patients with depression or chronic illness (Tomlinson et al., 2014). Exercise may reduce stress and enhance anti-inflammatory effects in tissues, leading to a putative association between exercise interventions and CRF reductions based on these mechanisms (Bower, 2019).

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3 Methodology

3.1 Research Design

The search strategy used to complete a structured literature review on the topic of cancer-related fatigue (CRF) in adults with cancer was presented, focusing on how physical therapy exercises contribute to the management of fatigue in this context. This focus is based on the lack of a structured synthesis of studies in the current literature base, which may limit the degree to which physiotherapists and other healthcare professionals can engage in evidence-based strategies to facilitate fatigue management. Details of the research strategy used, data analysis methods used, frameworks associated with analysis, synthesis, and justification based on the theoretical literature are provided.

A secondary approach was also used in this research. Several strategies can be used to facilitate secondary research, but the use of the literature method is particularly common (Creswell & Creswell, 2017). A structured literature review was adopted in this paper that included systematic approaches to data collection and analysis. Since the objective of the research sought to assess the effectiveness of the intervention, the use of a quantitative approach was considered the most valid means to address this objective. Quantitative research aims to establish measurable numerical associations between variables and thus provides an opportunity to determine the degree to which an intervention has a positive clinical impact (Jason et al., 2011; Hart, 2018). Therefore, the use of quantitative research was preferred within the structured literature review method.

The review question is formulated using a structured method that provides a detailed framework for identifying key aspects of the question that needs to be answered (Creswell & Creswell, 2017). The Population-Exposure-Outcomes (PEO) framework was used for this purpose, as it is a simple tool that can be effective in determining the parameters of key review questions (Bettany-Saltikov, 2012). The target population was patients with cancer-related fatigue, and the exposure/intervention of interest was the use of any form of physical therapy exercise that was directed by a physiotherapist or healthcare professional (that is, supervised physical exercise therapy). The result of interest was the effect of exercise on symptoms of cancer-related fatigue. These criteria were used to formulate the review question, as follows: Is physical therapy exercise effective in managing cancer-related fatigue?

Quantitative primary research studies were included according to the hierarchy of evidence (Murad et al., 2016). This favored the inclusion of randomized controlled trials (RCTs), quasi-experimental studies, and non-randomized cohort studies (Murad et al., 2016). Other forms of quantitative study (e.g. case studies and case studies) were excluded on the basis of a high risk of bias to assess the effectiveness of the intervention (LoBiondo-Wood & Haber, 2017).

The population of interest was people with an official diagnosis of cancer (any type and any stage), and therefore studies with people with other conditions were not eligible for inclusion in the review. All participants must be adults (18 years or older). Importantly, patients diagnosed with cancer should have evidence of cancer-related fatigue before starting the intervention, based on the presence of valid tools for assessing fatigue. Exposure/intervention was any form of physical therapy exercise carried out by the physical therapist. Ideally, studies should include data on adherence to the specified program to determine the validity of the intervention in influencing the measured outcomes; this was not a specific inclusion criterion, but was considered a potential feature of critical analysis of the literature. The results of interest were specific to the measurement of cancer-related fatigue. Quantitative measures of stress, including the use of validated tools and measures were necessary for inclusion, with at least one stress measurement recorded after the intervention. Use of alternative interventions or control conditions (eg standard care) were considered appropriate control conditions against which physical therapy exercises could be compared. There were no symptoms or other clinical findings of significance in the current review, and therefore studies focusing on these outcomes were excluded (with cancer-related fatigue analysis excluded).

3.2 Data collection and analysis

Quantitative studies of various methodological approaches were included in this research, so there was a need for a flexible tool that could assess specific features of each quantitative methodology (Buccheri & Sharifi, 2017). The Critical Assessment Skills Program (CASP) toolkit was used due to its flexible application to multiple study types and remarkable relevance to the research context (LoBiondo-Wood & Haber, 2017). CASP analysis results were used to exclude studies with significant methodological weaknesses or limitations from the final data set, and identification of specific limitations and weaknesses was used to guide critical discussion of the results of studies included in the final data set (Machi & McEvoy, 2016). So the official data mining tool was used for this purpose, using a tabular method. The main characteristics of each study (eg author, date, study design, demographics, details of the intervention (intervention method, length, frequency, severity, etc.)

4 Results

4.1 Electronic database search

A comprehensive literature search conducted in June 2020 based on the PEO framework resulted in a total of 204 studies across the PubMed, CINAHL, Scopus and Embassy databases. Polishing completed to PRISMA standards. Title analysis and abstract analysis resulted in the exclusion of 154 studies. Of the remaining 50 complete articles considered, 44 were excluded due to inappropriate methodological design (n = 22), lack of a measure of fatigue (n = 12), and lack of exercise supervision (n = 10). As a result, a final data set consisting of 6 studies was included in the research.

4.2 Methodological quality assessment

Assessment of methodological quality of the included studies was completed using the RCT-specific CASP tool. This decision was made because each of the studies adopted an RCT design. A summary of the critical appraisal findings for each study is presented in Table 3.1. Included studies were of a moderate (n=1) or high (n=5) level of quality, based on certain methodological weaknesses in research design and execution. Each RCT provided well-defined aims and objectives, and addressed a clearly focused issue. Every study showed clear evidence of randomised allocation of patients, with clear tracking of patients throughout the studies and accounting for dropouts from treatment or attrition in the obtained data. None of the included studies reported information regarding the blinding of either participants or assessors. Only one study noted that participants were blinded during the allocation of interventions but could not be blinded for the receipt of a behavioural intervention (Saarto et al., 2012). The CASP appraisal process indicates that the included studies were conducted and reported consistent with CASP's expectations of rigorous and scientifically robust research. Nevertheless, it should be noted that when examining some of the work in more detail, there were several exceptions. For example, effect sizes were not reported by the authors, despite their importance (Maher, Markey & Ebert-May, 2013), and despite the fact that reporting on them is part of best practices when publishing clinical RCTs (Appelbaum et al., 2018). It is also of note that studies such as Schuler et al. (2017) and Furzer et al. (2016) were inadequately statistically powered, hence giving rise to uncertainties around the veracity of their statistical results (Das, Mitra & Mandal, 2016).

Table 3.1 CASP appraisal overview

CASP question	**van Weert et al.**	**Saarto et al.**	**Andersen et al.**	**Steindorf et al.**	**Furzer et al.**	**Schuler et al.**
Focused issue?	Y	Y	Y	Y	Y	Y
Randomised?	Y	Y	Y	Y	Y	Y
Patient attrition?	Y	Y	Y	Y	Y	Y
Blinded?	N	N	N	N	N	N
Baseline similarity?	Y	Y	Y	Y	Y	Y
Equal treatment?	Y	Y	Y	Y	Y	Y
Treatment effect size?	Y	Y	Y	Y	Y	Y
Precision?	Y	Y	Y	Y	Y	Y
Applicable to local context?	Y	Y	Y	Y	Y	Y
Outcomes suitable?	Y	Y	Y	Y	Y	Y
Benefits worth harm and costs?	Y	N	Y	Y	Y	Y

4.3 Study characteristics

All included studies (n = 6) were randomized controlled trials (RCTs), each focusing on a clear assessment of CRF. An overview of authors, publication dates and titles is given in Table 3.2.

Table 3.2 Authors, dates, and titles of included studies

Author	**Date**	**Title**
Van Weert et al.	2010	Cancer-related fatigue and rehabilitation: a randomized controlled multicentre

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		trial comparing physical training combined with cognitive-behavioural therapy with physical training only and with no intervention
Saarto et al.	2012	Effectiveness of a 12-month exercise program on physical performance and quality of life of breast cancer survivors
Andersen et al.	2013	The effects of a six-week supervised multimodal exercise intervention during chemotherapy on cancer-related fatigue
Steindorf et al.	2014	Randomized, controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: results on cancer-related fatigue and quality of life
Furzer et al.	2016	A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients

4.3.1 Participants

1,207 participants were included in the 6 studies, with sample sizes ranging from 37 to 573. Patient populations included in the studies varied according to sociodemographic characteristics as well as the cancer diagnosis and stage of therapy or recovery. All patients were adults (aged 18 years or older) and had a formal diagnosis of cancer, and were either in receipt of therapy or had completed primary therapy for their cancer. Three studies included patients with any type of cancer (Andersen et al., 2013; Schuler et al., 2017; van Weert et al., 2010), while the remaining three studies focused on patients with haematological malignancies (Furzer et al., 2016) or breast cancer (Saarto et al., 2012; Steindorf et al., 2014). There was no discernible difference in age distributions across the included studies. In addition, there was no notable difference in gender distribution in studies, with the exception of breast cancer studies where only female participants were recruited (Saarto et al., 2012; Steindorf et al., 2014).

4.3.2 Fatigue measurement approach

In the included studies, fatigue was measured both at baseline and after interventions, but the measurement techniques used differed. The assessment scales used for CRF outcomes included the Multidimensional Fatigue Inventory (MFI) (Van Weert et al., 2010; Schuler et al., 2017), the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) (Saarto et al., 2012), the Functional Assessment of Cancer Therapy (FACT) (Andersen et al., 2013), and the Functional Activities Questionnaire (FAQ) (Steindorf et al., 2014). Furzer et al. (2016), unlike the other studies, triangulated their outcomes with the 36-Item Short Form Health Survey Questionnaire (SF-36), Aerobic Power Index (API), and Schwartz Chronic Fatigue Scale (CFS).

4.3.3 Intervention type and length of studies

All interventions used in the included studies involved an element of resistance training, while aerobic or cardiovascular exercise at varying levels of intensity were also associated with positive effects, particularly with respect to the physical aspects of fatigue. Several studies used a combination of aerobic or cardiovascular exercise and resistance exercise, although there was heterogeneity in the methods used to engage patients with this approach. The total length of the programmes used in these studies was typically between 6–12 weeks (n=5) [6 weeks (n=1) (Andersen et al., 2013), and 12 weeks (n=4) (van Weert et al. 2010; Steindorf et al., 2014; Furzer et al ,2016; Schuler et al. 2017)]. By contrast, Saarto et al. (2012) used a 12-month intervention programme. Only two studies, Saarto et al. (2012) and Furzer et al. (2016), incorporated within their design any meaningful follow up. These studies examined the impact of interventions at the 12-month and 24-week time points, respectively.

4.3.4 Control groups

The comparison or control groups differed across the included studies. Two out of six RCTs were three-arm (Furzer et al., 2016; Schuler et al., 2017) while the other four were two-arm (van Weert et al., 2010; Saarto et al., 2012; Andersen et al., 2013; Steindorf et al., 2014). The only study that provided a head-to-head comparison of different interventions programmes was Schuler et al. (2017), which compared supervised and unsupervised exercise. Despite this, within both groups that were studied in this RCT, the adopted exercises were the same and, therefore, determination of the most effective combination is not possible.

4.3.5 Dropout, adherence, and adverse events

While the reported dropout rate was unreported in one study (Andersen et al., 2013), it was reported as low in two others (van Weert et al., 2010; Furzer et al., 2016), 30% and 37% in Saarto et al. (2012) and Steindorf et al. (2014), respectively, and 60% in Schuler et al. (2017). In terms of adherence, the total adherence rates of patients in different groups across the included studies were varied. In several studies (n=4), including Steindorf et al. (2014) and Furzer et al. (2016), the adherence rates were high (at 97% and 91%, respectively). Andersen et al. (2013) reported a reasonable level of adherence at 73%, while the participants in van Weert et al.'s (2010) RCT had adherence rates of approximately 80%. In contrast to the above adherence rates, the average adherence to the prescribed exercise programme was 62% (32 hours out of 52 hours) in the study by Saarto et al. (2012). Regarding adverse events in the included studies, 5 of the 6 RCTs reported no adverse events during the interventions (Saarto et al., 2012; Andersen et al., 2013; Steindorf et al., 2014; Furzer et al., 2016; Schuler et al. , 2017). In van Weert et al.'s (2010) RCT, a single research participant died from cardiac arrest while engaging in the physical activity intervention, but the cause of death was unrelated to the exercise intervention.

4.4 Outcome

4.4.1 Quality of life

Quality of life (QoL) was an outcome measure in four RCTs (Saarto et al., 2012; Andersen et al., 2013; Steindorf et al., 2014; Furzer et al., 2016) Furthermore, these studies examined the relationship between the exercise interventions and QoL in the patients, and the results were mixed. Two of the studies reported on positive relationships between the exercise interventions and QoL (Steindorf et al., 2014; Furzer et al., 2016), while the remaining two studies did not find an improvement in QoL (Saarto et al., 2012; Andersen et al., 2013). Several QoL components improved as a result of exercise interventions in Steindorf et al. (2014), suggesting preliminary evidence for both the psychosocial and physiological benefits of physical activity. Steindorf et al. (2014) also found that substantial improvements in QoL and optimism for the future were significantly greater in the exercise treatment group. The study by Furzer et al. (2016) also reported on evidence for significant improvements in quality of life after exercise interventions. The other two studies reported inconsistent results. Andersen et al. (2013) identified no statistically significant relationship between the exercise intervention and QoL in the sample group of cancer patients across all levels of physical, emotional, social, and functional quality of life. Additionally, in Saarto et al. (2012), higher engagement in physical activity was associated with an increase in quality of life, but no relationship between the RCT's exercise intervention and quality of life was identified.

4.4.2 Fatigue

The only exception was the study of Saarto et al. (2012), which reported that there was no significant difference in CRF-related outcomes over the 12-month intervention period. Positive and statistically significant relationships were observed between fatigue and interventions in the other included studies. Furzer et al. (2016) found that aerobic and resistance exercises improved CRF compared to the control group (p=0.001) based on a combined evaluation using three fatigue scales: Schwartz Cancer Fatigue Scale (SCFS), vitality (VT), and Short Form Health Survey (SF-36). The researchers also reported that, at follow-up, those from the waitlist control who subsequently took up the intervention began to show improvements in their CRF-related outcomes. The RCT undertaken by van Weert et al. (2010) found that 2 hours of individual training plus group sports, with or without the addition of CBT, over 12 weeks was associated with significant improvements over usual care in the waiting-list control context (p<0.05). The findings suggested that there was very little difference between the use of exercise alone or exercise in combination with CBT. Both interventions were superior to the control condition in improving all domains of fatigue. Andersen et al. (2013) reported that 9 hours per week of supervised training involving cardiovascular, resistance, relaxation, and body-awareness training, including massage, over a period of 6 weeks led to a significant reduction in CRF. In Steindorf et al.'s (2014) research, 12 weeks of progressive resistance training improved global fatigue compared to the relaxation group (p=0.044), which was of the greatest significance for the physical fatigue sub-scale of the FAQ scale (p=0.013). Finally, Schuler et al.'s (2017) 12-week comparison of a combined cardiovascular/aerobic and resistance training programme relative to usual care indicated significant (p=0.01) improvement in global fatigue according to the MFI scale.

More detailed relevant results were also reported in Schuler et al. (2017), which are worth considering at this point in relation to the impact of the included studies' interventions on fatigue and CRF. In particular, the mean general fatigue score obtained in Schuler et al. (2017) using the MFI did not differ significantly between the three groups, although the values showed a nonsignificant trend supporting the use of any exercise-based therapy over standard care. Notably, the researchers found that the mental fatigue sub- scale of the MFI showed statistically significant reductions for any form of physical activity intervention compared with usual care (p=0.01), with supervised exercise interventions superior to unsupervised interventions (p<0.05). With the above results in mind, it is worth drawing attention to the fact that Saarto et al. (2012) was the sole study from the current review that provided no supportive evidence for the intervention that was trialled. However, other similar results were also reported in several of the included studies, such as Andersen et al. (2013) and Steindorf et al. (2014), insofar as certain types of fatigue (e.g., cognitive fatigue and motivational fatigue) did not fall as substantially as others (e.g., physical fatigue). In view of this, it is vitally important that statistically insignificant findings are reported within reviews, and so this study should not be discounted based on these results, but instead future work should seek to establish why a lack of impact occurred.

4.4.3 Long-term effects

Saarto et al. (2012) evaluated the use of a long-term exercise-based intervention which lasted for a total of 12 months. Although there was no additional follow up after 12 months, the authors argued that this was, nevertheless, a long-term study. Over the 12-month period of interventions, weekly sessions of supervised physical activity and support were delivered by a qualified physiotherapist in groups of 5 to 15 individuals. The results over the long-term period did not show any significant improvement in CRF between the treatment and control groups. The use of a follow-up period after the supervised intervention was noted in the study by Furzer et al. (2016). Following the initial 12-week exercise intervention, follow-up over a further 12 weeks was used to determine the persistence of exercise and effects on CRF. The findings showed that there were significant differences in CRF scores at 24-week follow-up between the two groups, consistent with data collected at 12 weeks. Importantly, during the same follow-up period, a group of patients with delayed uptake of the exercise intervention also showed significant improvements in CRF (p=0.001).

4.4.4 Effects of interventions on other outcomes

Given the lack of standardisation across the included RCTs' methodologies and research designs, each RCT addressed several outcome measures that others did not consider. For example, Schuler et al. (2017) examined blood albumin levels and other blood parameters, finding no significant difference between the intervention and control groups at the initial stage of the RCT. Saarto et al. (2012) assessed cardiorespiratory fitness before and after exercise interventions, reporting no significant impact. This result contrasted with Furzer et al.'s (2016) observation of a significant influence between the intervention and cardiovascular fitness, as well as the intervention and muscle strength. In addition to these outcomes, Saarto et al. (2012) evaluated neuromuscular performance, which improved significantly.

5 Discussion

The literature review structured in this search identified a total of 6 studies that fulfilled the inclusion criteria. Several key findings can be drawn from the available evidence referenced in this research: first, exercise-based interventions can reduce the CRF significantly, thus contributing to an improvement in quality of life; second, that supervised exercise-based interventions may have the greatest benefit compared to usual care or alternative active interventions without a supervised component in reducing CRF; Third, adherence to the intervention affects patient outcomes; Fourth, that the effectiveness of CRF exercise-based interventions can quickly lead to positive patient outcomes when patient adherence is high (sometimes producing positive outcomes in as little as several months); Finally, the lack of consensus on the definition and measurement of CRF hampers the development and analysis of clinical research.

As for the exercise method associated with the greatest benefit in the context of the CRF in this research, this was difficult to determine due to the reported heterogeneity of the included studies. For example, although evidence suggests that combined aerobic and resistance exercise may be beneficial in reducing CRF and promoting positive health, clear effects have also been observed with resistance training alone in breast cancer patients undergoing radiotherapy (Steindorf et al., 2014).). Likewise, the assessment of patients at different stages of the cancer journey, including during active treatment or post-treatment, complicates the possibility of advocating for one specific treatment option across this entire community. However, the use of individual approaches to treatment may be feasible and useful in this context and warrants further exploration in the literature to further refine these strategies.

Finally, with regard to adherence rates associated with randomized controlled interventions, some of the included studies had high adherence rates (n = 3), while others had moderate levels of adherence (n = 2). A low adherence rate of 62% was reported in Saarto et al. (2012), which was the lowest in all included studies. As this study included the longest intervention (12 months total), these results may indicate that patient adherence was related in an inversely proportional manner to the length of the intervention.

A systematic review and meta-analysis by Meneses-Echavez et al (2015), which included 9 research articles, reported findings similar to this review in terms of benefits of supervised exercise interventions for CRF. This was also the case for the more recent studies of van San Wu et al. (2019), Miguel et al. (2020) and Vulpen et al. (2020). Each study reported that the main benefits of supervised exercise interventions relate to enhanced adherence and opportunities for patient-centered care. These results are consistent with those of this review regarding greater benefits associated with supervised interventions compared to interventions lacking the supervised component.

The observation of this review and subsequent findings about the barrier to clinical research caused by the lack of consensus and the complexity associated with defining and measuring the CRF are consistent with the literature reviews by Mustian et al. (2018) and Burke et al. (2018). However, it is worth emphasizing that despite the challenges arising from this lack of consensus and the high level of complexity associated with definition and measurement, studies such as Ning et al. (2018) assert that clinical research into best practices surrounding CRF administration still has potential to advance and evolve, and the impediment may not be as substantial as the findings of this research suggest. From a policy perspective, research findings may not be robust enough to justify any changes in policy views and approaches to CRF management and post-treatment cancer care. A major policy driver in the context of cancer management in Scotland is the recently updated Beating Cancer: Ambition and Action report, which outlines the Scottish Government's strategy for cancer prevention, treatment and management initiatives (NHS Scotland, 2020). The latest update to the Long-Term Cancer Strategy outlined in the report identifies 53 clear actions that will be prioritized in the coming years, including screening, improving patient experiences, reducing inequality, and enhancing quality of life. These latter issues are of particular interest with respect to research findings, because the effect of physical activity in reducing CRF may improve quality of life, experiences of care, and broader overall outcomes.

6 Conclusion

Cancer is associated with a significant level of morbidity in affected individuals and places a significant burden on well-being and quality of life. Among the most debilitating features of cancer and cancer-related treatment is the presence of CRF. Evidence suggests that CRF can not only affect quality of life and functional status, but may be associated with a lower risk of survival. This structured literature review assessed the evidence base for the use of exercise-based therapy in the context of the CRF. Specifically, exercise that was regulated and directed/supervised by physical therapists or other healthcare professionals was explored, as study data indicated that exercise may modulate inflammatory processes and could lead to clinical improvement in CRF symptoms (Bower, 2014).

Differences in the types of exercise programs evaluated in the research literature were a significant source of heterogeneity, along with cancer type, cancer treatment or stage of recovery, and outcomes evaluated. While the general findings indicated that exercise supervised by physical therapists or other members of the health care team was an effective intervention, a specific exercise program cannot be recommended across the population due to the lack of direct comparisons. The use of aerobic exercise and resistance or strength training has been more commonly evaluated and may represent a combination that correlates with overall effects on well-being (Schuler et al., 2017). Although this review was intended to be comprehensive in nature, limitations in the quality and quantity of evidence collected and synthesized are notable. Therefore, further research is needed to clarify remaining uncertainties regarding the value of exercise-based therapy for CRF. There is a need for research focused on establishing the optimal exercise program used in patients with CRF, including methods for precisely tailoring programs to the needs and capabilities of patients with different types of cancer. There is also an important need for research to compare exercise-based interventions in a face-to-face format. This should be completed using robust RCT methodology and may include comparisons of exercise duration and intensity, as well as different methods of exercise when applied to the same group of

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patients. Finally, based on observations from the literature scope review conducted by the researcher in preparation for this research, it is recommended to use qualitative studies to explore aspects of implementation and adherence to supervised exercise-based strategies in the context of the CRF. Such studies may complement quantitative data in identifying potential barriers to the efficacy and feasibility of exercise-based interventions in practice, providing a basis for hypothesis generation and subsequent testing of strategies to overcome identified barriers in future studies.

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