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Litterature review

Bachelor's thesis in Human Movement Science
Supervisor: Tom Ivar Lund
March 2024

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Abstract

The cancer disease has for a long time affected many people worldwide. With continuous advancements in medicine and modern technology, there are more cancer survivors than before. Patients are likely to experience long-term side effects from treatment, with chemotherapy-induced peripheral neuropathy (CIPN) being one of the most difficult to treat. Despite the absence of effective cures for CIPN, emerging evidence suggests that physical activity may give relief from the symptoms. However, research investigating the effects of exercise on these long-term side effects remains limited. Therefore, this literature review aims to explore the impact of physical activity and exercises on CIPN in cancer patients during or after chemotherapy treatment. Eight of the 91 studies from PubMed were included in this analysis. The findings indicate that multi-modal exercise interventions may have the greatest potential for alleviating CIPN and its detrimental impacts during chemotherapy. Additionally, enhancing chemotherapy tolerance. Thus, with these results, future research should focus on optimizing exercise regimes, exploring long-term effects after chemotherapy ends, and determining the most functional exercise for different cancer types.

Abstrakt

Kreft diagnosen har lenge berørt mange, men med dagens medisin og teknologi er det flere overlevende enn før. Likevel opplever pasienter langvarige bivirkninger fra behandling. Cytostatika-indusert perifer nevropati (CIPN) er en av de mest vanlige bivirkningene som oppstår etter kjemoterapi, samt utfordrende å behandle. Dette fordi det ikke enda finnes en effektiv kur, samt lite forskning på forebyggende og motvirkende tiltak mot symptomene. Til tross for dette har en rekke studier vist at fysisk aktivitet og trening kan lindre og dempe symptomene. Derfor skal dette studiet utforske effekten fysisk aktivitet og trening har på CIPN hos kreftpasienter som har gjennomgått eller har fullført kjemoterapi behandlingen. Et litteratursøk med utvalgte søkeord ble gjennomført i databasen PubMed. Søket resulterte med 91 artikler, hvor åtte ble inkludert på bakgrunn av forhåndsbestemte kriterier. Funnene viste at en kombinasjon av ulike treningsformer var mest effektivt for lindring og motvirkning av CIPN-symptomene under kjemoterapi behandlingen. Derfor bør fremtidig forskning fokusere på å optimalisere treningsregimer, utforske langtidseffekter etter kjemoterapi er avsluttet, samt evaluere hvilken treningsform som gir best effekt for de ulike kreftformene.

Keywords: Chemotherapy drugs • cancer patients • impact • nerve damage • physical training

1. Introduction

Cancer is a disease that has affected many people worldwide for a long time and it is continuing to experience a trajectory due to longer lifespans (1). Although the disease is a leading cause of death, there is hope in the realm of cancer care due to continuous advancements in medicine and modern technology. New methods for early cancer detection and increasingly effective treatments have contributed to a rising number of cancer survivors (1). Chemotherapy drugs, for instance, slow down and stop the progression of cancer by targeting and eliminating rapidly dividing cells. However, the drugs cannot always differentiate between cancerous and non-cancerous tissue and often damage the healthy, rapidly dividing cells. After chemotherapy, patients may experience a reduced quality of life due to the negative side effects from the treatment, such as chemotherapy-induced peripheral neuropathy (2).

Chemotherapy-induced peripheral neuropathy (CIPN) occurs due to damage to the peripheral nerves outside the brain. This condition commonly results in numbness and pain, typically affecting the hands and feet, but also other areas and body functions (2). This refers to deficits in sensory and motor skills leading to inappropriate proprioceptive feedback, impaired postural control, and fall risk (3). The occurrence of CIPN varies based on the specific chemotherapy drug and the dose used, with reported rates ranging from 19% to 85% (4). According to other articles, CIPN additionally results in broader societal implications, leading to economic burdens on patients and financial strain on healthcare professionals and hospitals (5).

Currently, there is no single effective method of preventing CIPN, and treatment possibilities are limited (2). However, based on a growing body of studies, physical activity has been suggested as a possible intervention in the limited treatment options for CIPN (6). Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. It is categorized into occupational-, sports-, conditioning-, household- and other activities. A subcategory of physical activity is exercise. Exercise is planned, structured, repetitive, and purposive actions. Aimed to enhance or preserve different aspects of physical fitness. Physical fitness is a set of attributes that individuals possess or aspire to achieve. The definition of physical fitness falls into two groups. One focuses on health-related aspects, such as cardiorespiratory endurance, muscular strength, and flexibility. While the other is more related to athletic skills connected to a specific sport (7).

One could argue that patients may experience an absence from engaging in regular physical activity, considering the long-term side effects. However, physical activity is associated with a better health-related quality of life, along with less pain, fatigue, and mental distress among cancer survivors (8). Additionally, research says that engaging in physical activity may decrease cancer mortality rates. Research also suggests that individuals who are more physically active have a lower risk of later developing peripheral neuropathy (9).

Therefore, this literature review aims to study the effect physical activity and exercise have on chemotherapy-induced peripheral neuropathy among cancer patients.

2. Methods

For this literature review, we conducted a search using PubMed. The detailed search strategy is outlined in Table 1 and resulted initially in 92 articles. To align with our objectives, filters such as randomized controlled trials from 2000 to 2024 were added, resulting in 20 articles from the years 2013 to 2024. The title and abstract of these articles were reviewed for relevance. To further refine the selection, specific inclusion and exclusion criteria, presented in Table 2, were applied. Subsequently, the remaining papers were thoroughly examined, resulting in eight remaining articles. The screening process is presented in Figure 1.

Table 1: *Search strategy on PubMed*

Search number	Search term
Search #1	"Physical activity (MeSH) OR "exercise" (All Fields) OR ("physical activity*" (All Fields) AND "activity" (All Fields)) OR "physical activity" (All fields)
Search #2	"Cancer patients" OR cancer´s patient´s (All fields)
Search #3	"chemotherapy" OR "chemotherapy* (All fields) OR (MeSH) "drug therapy" (All Fields) OR "chemotherapies" (All fields)
Search #4	"Peripheral neuropathy" OR (MeSH) "peripheral nervous system diseases" OR ("peripheral" (All fields) AND "nervous" (All fields) AND "system" (All Fields)) OR "peripheral neuropathy (All fields)
Search #5	"effects" OR "effect*" (All fields)
Search #6	Search #1 AND search #2 AND search #3 AND search #4 AND search #5

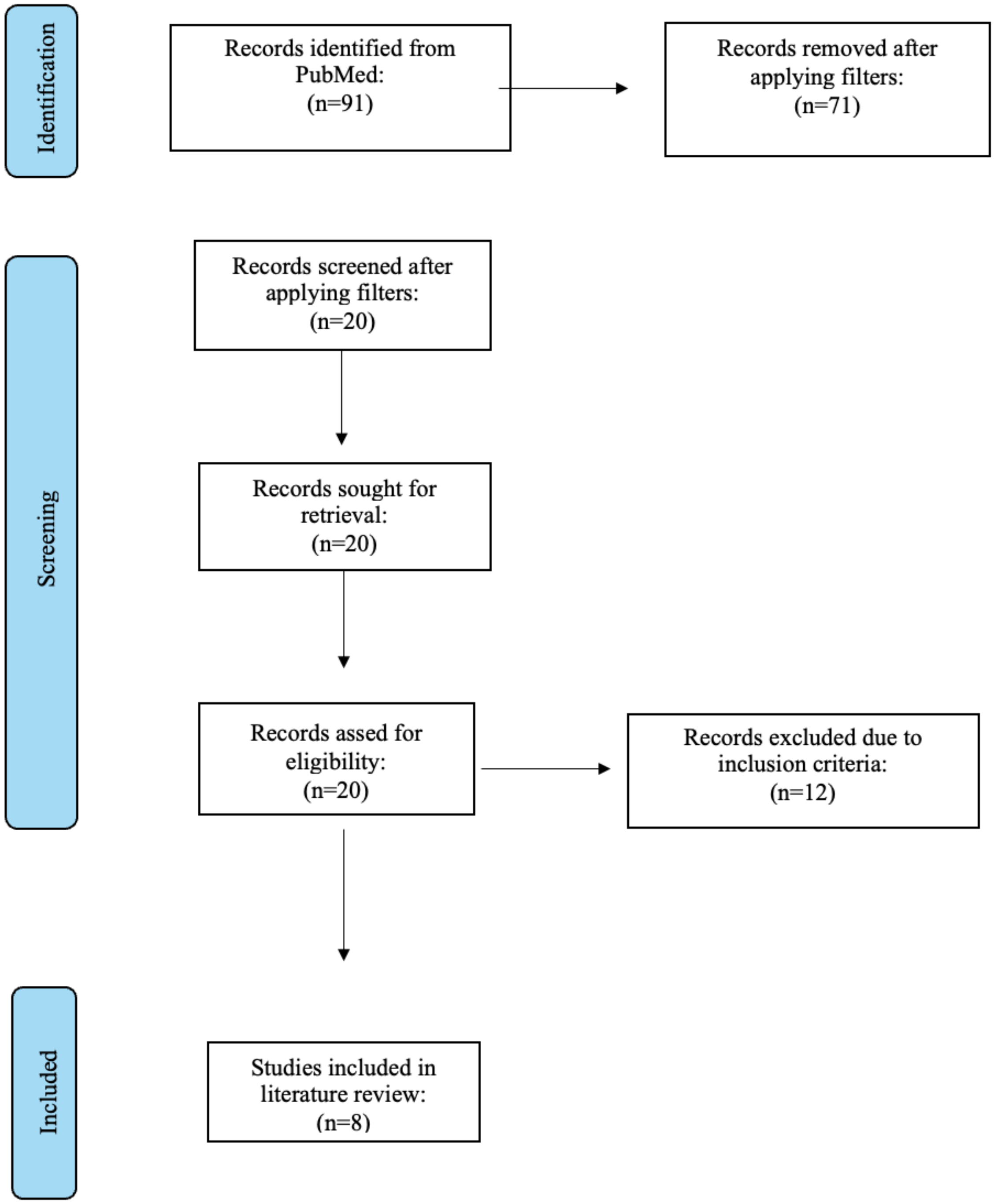
MeSH: Medical subject headings

Table 2: *Inclusion- and exclusion criteria*

Inclusion criteria	Exclusion criteria
Cancer patients	Other diseases
During or post- chemotherapy	Pre-chemotherapy
Only RCT studies	Other study designs then RCT
English or Norwegian language	Other languages than English or Norwegian
Adults	Children, youth, or young adults
Free full text	Requires payment for full text
Physical activity or exercise as intervention	

RCT: randomized controlled trials. CIPN: chemo-induced peripheral neuropathy

Figure 1: *Illustration of the screening process*



3. Results

3.1 Analysis of literature

This literature review included eight studies with a combined recruitment of 727 participants, 595 females, and 102 males. The gender of 30 participants is unknown. The number of participants in each study ranged between 27 to 355. Table 4 presents the sources, groups, and numbers of participants, mean age and standard deviation, and results. The eight studies originated from five different countries, three from Germany, two from India, one from the United States, one from Columbia, and one from Thailand.

Table 4: *Overview of main results*

Source (author, year)	Groups and no. of participants (n)	Mean age ± SD	95% Confidence interval	P-value
Kleckner et al., (2018)	EG: (n) = 170 CG: (n) = 185 Total: (n) = 355	EG:55.6± 11.8 CG: 55.9± 9.7	Main effect of exercises vs control Numbness and tingling: -0.42 (-085,0.02) Hot/coldness in hands/feet: -0.46 (-00.01, -0.91)	Numbness and tingling: *p*=0.061 Hot/coldness in hands/feet: *p*=.045
Zimmer et al., (2018)	IG: (n) = 17 CG: (n) = 13 Total: (n) =30	IG: 68.53± 9.23 CG: 70.00± 5.56	N/A	Changes over time (IG vs CG) T1-T0 T2-T0 Bench press: *p*=.014, *p*=.014 Leg press: *p*=.001, *p*=.011 Lat pulldown: *p*=.022, *p*=.031 Neuropathic pain: *p*=.023 CIPN: *p*= .045
Dhawan et al., (2020)	EG: (n)=22 CG: (n)=23 Total: (n) =45	EG: 50.5± 7.9 CG: 52.5± 6.6	Neuropathy symptom experience score: 3.19 (-18.3,24.7) Neuropathy interference score: 0.8 (-6.5,8.1)	EG vs. CG Neuropathy symptom experience score: *p*<.001 Functional QoL: *p*=.0002 Symptom QoL: *p*=.0003
Saraboon et al., (2021)	BG: (n) = 15 CG: (n) = 15 Total: (n) = 30	BG: 45.07 ± 3.88 CG: 45.53 ± 4.64	4 weeks vs 6 weeks FAB score: -2.10 (-4.20, -0.11) vs -3.30 (-5.40, -1.20) Baseline vs 6 weeks FACT-Taxane: 1.3 (-6.20,8.70) vs -6.4 (-14.0,1	BG vs CG FAB scores: *p*=.04, *p*<.01 FACT-Taxane: *p*<.01

Kneis et al., (2019)	IG: (n) = 22 CG: (n) = 19 Total (n) = 37	IG: 70 ± 6.16 CG: 60 ± 5.38	IG vs CG STSP (mm): -76 (-141- -17) vs -6 (-52-50) PJ (W/kg): 0.3 (-0.9-1.6) vs 1.3 (0.2-2.2) JH (cm): 1 (-0.4-3.2) vs 2 (0.5-3.5) CIPN20 sum score: -10 (-17- -4) vs -6 (-11- -1) CIPN 20 sensory score: -7 (-15-0) vs -7 (-15-0) CIPN motor score: -8 (-18-0) vs -2 (-6-2) MPO: 0.2 (-1.7-1.7) vs 1.4 (-0.4-3.5)	IG vs. CG STSP (mm): *p*=.049 PJ (W/kg): *p*=.019 JH (cm): *p*=.045 CIPN20 sum score: *p*=0.007, *p*=.027 CIPN20 sensory score: *p*=.028, *p*=.018 CIPN20 motor score: *p*=.006, *p*=.014 MPO**:** *p*=.025, *p*=.004
Streckmann et al., (2019)	SMT: (n) = 10 WBV: (n) = 10 CG: (n) = 10 HCG: (n)= 10 Total: (n) = 40	SMT: 56± 8.23 WBV: 59± 5.63 CG: 59±6.49 HCG: 57± 6.49	N/A	IG vs CG ASR: *p*=.017 PSR: *p*=.020 PDS: *p*=.010 Pain: *p*=.043 QR: *p*=.054
Müller et al., (2021)	SMT: (n) = 49 RT: (n) = 57 UC: (n) = 57 Total: (n) = 163	SMT: 51.7±10.8 RT: 53.4±11.7 UC: 54.5±11.9	Per protocol SMT+RT: -8.3 (-16.1 to -0.4) MS: +20.8 (11.2,30.4) QoL: +12.9 (3.9,21.8)	IG vs. UC AE: *p*=0.039-0.045 MS: *p*<0.001 QoL: *p*=0.005
Bland et al., (2019)	IE: (n) = 12 DE: (n) = 15 Total: (n) =27	IE: 51.0± 8.1 DE: 49.5± 1.1	N/A	Main effect IE vs DE Numbness in toes or feet: *p*=.04 Impaired vibration sense in the feet: *p*<.01 CIPN20 sensory: *p*<.01 Motor symptom scores: *p*<.01

EG: exercise group, CG: control group, SD: standard deviation, IG: intervention group, N/A: not applicable, QoL: quality of life, BG: balance exercise group, FAB score: Fullerton Advanced Balance, FACT-Taxane: Functional Assessment of Cancer Therapy, STSP:ST_{eo} sway path, PJ: P_{max_jump} , JH: jumping height, MPO: maximum power output, SMT: sensorimotor training, WBV: whole- body vibration training, HCG: healthy control group, ASR: Achilles tendon reflex, PSR: Patellar tendon reflex, PDS: Peripheral deep sensitivity, QR: questionnaire, RT: resistance training, UC: usual care, MS: muscular strength, AE: Adherent exercise, IE: immediate exercise, DE: delayed exercise.

3.2 Study interventions

The eight analyzed articles included participants with various types of cancer and drug treatments, with breast cancer and taxane drugs being the most common. All articles included either two- (one exercise group and one control group), three- (two exercise groups and one control group), or four groups (two exercise-, one control and one healthy control group). Seven out of eight studies consisted of both males and females. One only studied female participants. The control groups received either conventional therapy, usual care, or endurance training. Ten different intervention groups were investigated, encompassing several types of exercise. Six of eight studies did their research on participants undergoing chemotherapy. One researched both during and post-chemotherapy, and the other one researched only after chemotherapy. To evaluate CIPN symptoms among the patients, a mix of patient-reported outcomes such as quality-of-life assessments, and specific neuropathy-focused questionaries was employed. Some studies also performed clinical tests such as vibration sense and pinpricking.

The three studies by **Kleckner, Zimmer, and Dhawan et al., (10-12),** examined the impact of multimodal and supervised exercise programs compared to usual care on CIPN symptoms in colorectal-, breast -, and lung cancer survivors. The exercises consisted of progressive walking, endurance-, resistance-, and balance training. **Kleckner et al., (10)** studied a sample size of 355 participants randomized into an exercise- and control group. The exercise group reported fewer severe CIPN symptoms compared to the control groups in pre-intervention. Specifically, numbness and tingling (coefficient-0.42, CI=-085,0.02, p=0.06) and hot/coldness in hands/feet (coefficient=-0.46, CI=-0.01, -0.91, p=0.045) reduced with exercise, indicated by the negative coefficients. Furthermore, a trend-level effect was observed, suggesting that older patients benefited more from exercising than younger patients (p=0.086). Males also exhibited a better response to exercise than females (p=0.076). Additionally, those with breast cancer had better responses from exercises compared to participants with other cancer types (p=0.076).

Zimmer et al. (11) conducted a smaller sample size including 30 participants. According to the results, the neuropathic symptoms remained consistent over time in the intervention group (p=.023). For the control group, CIPN significantly worsened before and after the trial, and after a four-week follow-up (p=.045). Unlike the control group, the intervention group improved in strength and balance function (*p=.048)*. However, no differences were found between groups regarding patient´s endurance capacity. Additionally, changes in CIPN correlated with balance changes (*p*=.022, *p*= .006). **Dhawan et al., (12)** also studied a small sample size with 45 participants who were experiencing CIPN symptoms. In this study, the experimental group received a higher dose of chemotherapy drugs. The results showed a significant reduction in neuropathic pain scores (coefficient: 3.19, CI=-18-3,24.7) and CIPN interference scores (coefficient: 0.8, CI=-6.5,8.1). Moreover, compared to the control group, there was a significant improvement in the mean scores for functional-, *(p*=-0002)*,* symptom-, (*p*=.0003), and global health status quality of life (*p*=.004). The study additionally discovered that males experienced higher functional outcomes and reported fewer symptoms compared with females.

Saraboon and **Kneis et al., (13,14)** investigated in their studies the impact of balance exercises on physical performance, peripheral neuropathy symptoms, and quality of life in diverse cancer populations. In **Saraboon et al.´s (13)** study, the control groups experienced a decreased balance performance at four weeks and six weeks ($p<0.001$ and $p<0.0001$, respectively), while the balance exercises group remained stable. A between-group comparison during these weeks revealed significant differences in balance scores (*p*=0.04 and *p*=<0.01). However, no significant differences were observed in the functional assessment of cancer therapy between the balance exercises-, and the control group. Presented with a decrease ($p<0.01$) and an increase ($p<0.01$) at six weeks.

In **Kneis et al.´s study (14)**, the intervention groups engaged in both balance-, and endurance training. Assessments encompassed functional performance, cardiorespiratory fitness, vibration sense, and self-reported symptoms related to CIPN. Results showed that the intervention groups reduced their sway path during semi-tandem stance (coefficient: -76, CI=-141- -17), and patients also reported decreased motor symptoms (coefficient: -8, CI= -18-0). Both groups reported a reduction in overall CIPN-, (coefficient: -10, CI= -17 – -4; control group: -6, CI -11 – -1) and sensory symptoms (coefficient: -7, CI= -15 – 0). Additionally, maximum power output was strengthened in both groups (IG and CG coefficient: 0.1 W/kg, CI= 0.0–0.2), although only the control group improved their jump height (coefficient: 2 cm, CI= 0.5–3.5).

Both **Streckmann and Müller et al., (15, 16)** studied the efficacy of sensorimotor exercise and other types of exercises on patients experiencing CIPN symptoms. Both studies inclusively compared the exercise intervention groups with a usual care or control group. Streckmann et al., (15) examined sensorimotor-, (SMT) and whole-body-vibration training (WBV) after chemotherapy treatment, whilst Müller et al., (16) examined sensorimotor- and resistance training during chemotherapy treatment.

Müller et al., (16) consisted of a sample size with 159 participants. The analysis regarded an intention-to-treat (ITT) and per-protocol analysis (PP), where ITT revealed no differences regarding CIPN signs/symptoms. PP analysis indicated that subjectively perceived sensory symptoms in the feet increased less during chemotherapy in the adherent exercises (coefficient -8.3, CI=-16.1-0.4, p=.0039). Adherent exercise additionally received a higher relative chemotherapy dosage but improved muscular strength (coefficient: +20.9, CI: 11.2-30.4, p<.001) and quality of life (coefficient: +12.9, CI= 3.9-21.8, p=.0005). **Streckmann et al., (15)** consisted of a smaller sample size with only 40 participants, focusing mostly on the effect of balance training. The SMT group consisted of progressively more difficult balance exercises than the WBV group. Like Müller et al., (16), Streckmann et al., (15) also studied patients' quality of life intently through a standardized questionnaire, indicating improvement of symptoms (p=.054). No 95% confidence interval was observed in the study of Streckmann et al., (15), however, significant differences were found for Achilles and patellar tendon reflexes (p=.017, p=.020), peripheral deep sensitivity (p=.010), and pain (p=.043).

Bland et al., (17) was one of the studies that investigated the effect of exercise on CIPN both during and post-taxane treatment. Compared to other studies Bland et al., (17) included a smaller sample size with only 27 females treated for breast cancer. Participants were randomly assigned to either immediate exercise during chemotherapy or delayed exercise after chemotherapy. The p-values revealed significant differences between the groups with various measures related to neuropathy, indicating positive effects from exercising. Participants in the immediate exercise group reported a lower incidence of numbness in toes and feet compared to the delayed exercise group (p=.04). This group additionally reported better sensory function, supported by lower scores on the CIPN sensory scale (p<.01). Motor symptoms scores were notably lower in the immediate exercise group compared to the delayed exercise group (p>.01). Despite differences, both groups experienced worse sensory- and motor symptom scores, relative to baseline measurements (p<.01). As immediate exercise intervention may offer certain advantages in terms of mitigating specific CIPN symptoms, no differences between the groups were found by the end of chemotherapy. This applied to severe numbness in the toes or feet (p=1.0) or impaired vibration sense in the feet (p=.71).

4. Discussion

The eight studies in this literature review examined physical activity's impact on CIPN among cancer patients. All showed that exercise interventions had promising effects in preventing and alleviating CIPN symptoms. Notably, Dhawan, Kneis, Streckmann, and Müller et al, (12, 14-16) recruited participants who experienced CIPN. Whether Kleckner, Zimmer, Saraboon, and Bland et al., (10,11,13,17) studied participants without CIPN symptoms for prevention or those who experienced CIPN for counteraction is unknown.

Of the eight studies, the ones including balance and endurance training showed the most efficient results between the intervention and control groups. We also noticed that interventions that combined different exercises, such as endurance-, resistance, balance-, and sensorimotor training, had more beneficial outcomes. Exercise interventions, ranging from progressive walking and resistance exercises in sensorimotor and balance training inclusively showed promising results in alleviating CIPN. To further optimize the exercise program, additional factors such as the severity of neuropathy, individual patient preferences, and the goal of treatment should be considered.

Commenting on balance, and sensorimotor exercise, another study by Taube et al., (18) proved that these interventions played a crucial role in addressing postural instability. Especially in populations with proprioceptive deficits such as patients with CIPN. In our literature review, six of eight studies researched balance and sensorimotor exercise, and how proprioceptive deficit affects postural instability. Additionally, why it is important to train these aspects for a patient affected by CIPN. Kneis et al., (14) emphasized the importance of balance training, as it leads to neuronal adaptations and improved muscular output, giving the patient better postural control. Engaging in balance exercises involves interaction between sensory input from different systems in the body. Combining balance exercise with other types of exercises has been proven to stimulate and improve these physiological aspects. Kneis et al., (14) further observed improvements in both groups indicating that exercise intervention also targeted other aspects of CIPN, such as pain management and enhancing quality of life.

Streckmann and Müller et al. (15, 16), also proved that engaging in sensorimotor exercise improves patients' proprioception, balance, coordination, and motor control. These physiological benefits may affect empowerment and self-management. In other words, as patients learn and practice sensorimotor and balance exercises, it empowers them to take an active role in managing their symptoms, causing a sense of self-efficacy and control. Both studies found significant CIPN benefits, which may be due to the employment of clinical- and patient-reported outcomes to confirm chronic CIPN.

During chemotherapy, muscle area significantly decreases, worsening negative side effects like fatigue (10). However, endurance or aerobic exercise has been shown to improve mitochondrial function in skeletal muscle and possibly influence the mitochondria in nerve cells (20). In addition, resistance exercises delay the loss of muscle mass (21). According to other studies, it is believed that exercises can alleviate CIPN. Improving vascular function and metabolic activity in peripheral nerves, boosting neurotrophic factors, and reducing inflammation (22). Kleckner et al. (10), outlined the potential of reducing chronic inflammation and influencing brain processes though exercises. These mechanisms suggest that exercises might help reduce the increased sensitivity in the central nervous system linked to nerve-related pain, like in CIPN. The results suggest that individuals who engage in more physical activity and possess greater muscle mass tend to experience less severe symptoms of CIPN (10).

Kleckner et al. (10) further identified that exercise effectiveness in treating CIPN symptoms varies with age, being more effective in older patients. Exercise can change the brain to reduce nerve-related pain regardless of its origin, potentially protecting against chemotherapy side effects. In other words, engaging in regular exercise may help preserve certain neural pathways responsible for processing awareness of sensory information as people age. This preservation could potentially benefit older individuals who are undergoing chemotherapy. As it protects them from the negative effects of chemotherapy on the nervous system, thus reducing the symptoms associated with CIPN. Low to moderate intensity exercise may serve as a protective factor against such aspects (23). Knowing these factors can help healthcare providers create exercise plans that fit each patient's characteristics. Additionally, it could help preserve neural pathways involved in sensory processes. Future research should potentially focus on studying homogeneous groups, as age along with other factors will affect the intensity, duration, and amount of exercise.

Despite exercise interventions effectively alleviating neuropathic symptoms and enhancing strength, Zimmer et al (11) observed no improvements in endurance capacity. This lack of improvement might be because the control groups got better at the test simply by doing it multiple times compared to the intervention group. The six-minute walk test serves as a common tool for assessing function status but may not fully capture endurance capacity (11). Hence, further studies could benefit from employing more precise tests like spiroergometric assessments. Nevertheless, targeting endurance at 60-70% of maximum capacity remains crucial in exercise programs. Cardiorespiratory fitness is identified as a predictor of survival in patients with metastasized colorectal cancer (11). Therefore, more research should focus on finding ways to improve the endurance capacity of other cancer types and longer endurance sessions may be necessary. Despite these limitations, the patients in the study still only reached about 73.43% of the expected health levels at baseline, and 77,1% after. This suggests that they still had functional limitations even after exercising.

Bland et al. (17) found no differences in symptoms from the standardized quality of life questionnaire. However, other patient-reported outcomes proved that exercises during chemotherapy slowed the worsening of certain nerve-related symptoms after three treatment cycles. Which further enhanced overall quality of life and chemotherapy tolerance. This potentially reduces the need for dose reductions or treatment cancellations. With limited recommended treatments for taxane chemotherapy-induced nerve pain and weak evidence for alternative therapies, exercises emerge as a viable option. This is supported by the studies suggesting their efficacy in easing nerve-related pain and aiding chemotherapy completion. Exercising could additionally counteract CIPN by improving vascular function, metabolic activity, and neurotrophic factors, with multi-modal exercise interventions as the most promising.

The current evidence does not permit definitive conclusions regarding the positive impact of exercises on chemotherapy tolerance (19). However, the results from Bland et al. (17), align with those of Müller et al., (16) and suggest a promising avenue for further exploration. Despite some studies showing immediate improvement during chemotherapy or shortly after, it is important to notice that the long-term effects of exercise intervention were not always observed in our studies. Therefore, future research should focus on assessing the sustained benefits of exercise interventions after chemotherapy ends.

Kleckner and Dhawan et al., (10, 12) also observed differences in response to exercises between male and female participants. Male participants had higher functional outcomes and reported fewer CIPN symptoms compared with females. This could be explained by biological factors, such as hormonal, muscular, and metabolic differences. For example, men generally have higher levels of testosterone compared to women. This gives males a better advantage in building bone strength and increasing muscle mass. Furthermore, it was observed that females with breast cancer had better responses from exercises compared to patients with other cancer types. However, this was not thoroughly commented enough on in the studies. Future research should therefore explore the physiological differences between genders, and cancer types, as these aspects could potentially affect the results of exercising.

4.1 Biases and limitations

The lack of statistically significant differences among the studies may be attributed to various factors. Small sample sizes, as seen in six of eight studies, limit the generalizability of the findings to a broader population. A larger sample size, as seen in Kleckner and Müller et al., (10,16), could provide more robust evidence of exercise intervention. In addition, all studies were conducted with adults whose physical activity or fitness was generally below average. Another limitation in our review was the type of cancer and drug investigated, as most studies focused only on one type of cancer and chemotherapy drug (10, 11, 12, 16). This may affect the overall relationship between exercising and CIPN symptoms, as various types of cancers and drugs were not studied.

Moreover, while RCT aims for randomization, there may still be selection biases between groups, as observed in Kleckner et al. (10). Additionally, high dropout rates, as noted by Müller et al. (17), could affect the validity of the results, as dropouts may differ from those who complete the study. The advantage of using per-protocol analysis for this case is that it excludes confounding effects of non-adherence or protocol violations, focusing only on answering the problem. However, only performing a per-protocol analysis could lead to limitations such as smaller sample sizes and loss of randomization. Additionally, patients in a per-protocol analysis may be more motivated or compliant, leading to better outcomes and could potentially overestimate the true treatment effects.

We additionally noticed a lack of data regarding the efficacy of exercise treatment in post-chemotherapy. Streckmann et al. (15) was the only article studying the effect of physical activity and exercise after chemotherapy treatment. Additionally, Bland et al., (17) studied the efficacy both during and after chemotherapy. Both articles revealed that physical activity and exercise had a positive effect on CIPN symptoms. This aspect should therefore be considered in future research to determine whether exercise could be beneficial for managing CIPN symptoms, not only weeks, but also months and years after therapy has ended.

Kleckner, Zimmer, Streckmann, and Müller et al. (10,11,15, 16) measured CIPN symptoms through subjective measurements of standardized questionnaires. Such measures could be seen as a recall bias as it is influenced by the individual. Objective measures through clinical testing could provide more accurate data but are more resource consuming. In practical terms, performing both objective and subjective measures is recommended for more reliable outcomes. Bland et al., (17) for example performed standardized questionnaires with clinical tests to evaluate the patient's experience of CIPN symptoms. Such approaches could potentially amplify the validity of whether exercise has an impact on CIPN symptoms through different stages of treatment.

Lastly, our literature review met some limitations through the search strategy. Narrowing the literature search led to both positive and negative outcomes. Positively, it narrowed the search enough to only reach the most efficient results for answering our thesis statement. On the other hand, narrowing a search may exclude valuable information regarding findings. This was observed in our primary studies, as almost all studies focused on the same future recommendations, referring to dosage, long-term treatment, and bigger sample sizes. Additionally, only investigating RCT studies may exclude literature focusing on other aspects such as homogenous groups for example. Our purpose was to investigate the effect physical activity and exercise have on CIPN, and almost all the articles we studied proved this. However, this can also be seen as a publication bias as studies with positive findings are more likely to be published than studies with negative findings. This could potentially affect the validity of our study, as there were only a few articles that reported low to no effect from exercising. Nevertheless, most of the studies included in this literature review did discuss biases and limitations. This provided us with enough information on whether physical activity and exercise are worth mitigating into therapy for preventing and countering CIPN symptoms.

5. Conclusion

To conclude this literature review, all eight studies highlighted the potential of performing physical activity and exercise as a part of therapy for alleviating and counteracting CIPN symptoms among cancer patients. Balance-, and endurance training showed the most efficient results between intervention and control groups. However, our findings suggest that physical activity and exercise, combined- or in different forms may give the most beneficial outcomes. In practical terms, healthcare professionals are encouraged to prescribe physical activity and exercise as an additional component to cancer treatment for reducing CIPN symptoms and pain. Further research should assess the sustained benefits of exercise interventions as a part of long-term follow-up and determine if improvements in symptoms persist over time. It is also recommended to identify which exercise is the most effective for the specific cancer type. Such findings may motivate patients to take a more active role in treatment and managing their symptoms, improving their quality of life.

6. References

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