Tesis Doctoral Internacional / International Doctoral Thesis

Prevención con restricción del flujo sanguíneo sobre la incidencia de toxicidad neural en cáncer de mama (PRESIONA): ensayo clínico controlado y aleatorizado durante quimioterapia neoadyuvante

Prevention with blood flow restriction on peripheral neurotoxicity in breast cancer (PRESIONA): randomised controlled clinical trial during neoadjuvant chemotherapy

Programa de Doctorado en Medicina Clínica y Salud Pública

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Al Gen ***Chop*** que, aunque sea el representante de la apoptosis,

para mí es vida.

INDEX

ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity for many commonly used anticancer agents. It is generated by axonal and dorsal root ganglion damage, predominately is a sensory neuropathy and may influence survival and quality of life. Physical exercise programs appear to be feasible and effective at reducing CIPN symptoms. However, in fact, so far CIPN treatment still no cure and lacks robust evidence both for pharmacological and non-pharmacological. Thus, the impact of CIPN has led researchers and clinicians to question which dose of physical exercise is more suitable in patients with cancer for prevention of CIPN. This Doctoral Thesis aims to contextualise the state-of-the-art of physical exercise to prevent CIPN in patients with cancer (**Study I**) and to propose a physical exercise program plus blood flow restriction (BFR) with the capacity to prevent neuropathy (PRESIONA) (**Study II**).

For **Study I**, a systematic review with meta-analysis was carried out to analyze the effects of physical exercise applied before or during chemotherapy to prevent or ameliorate CIPN in randomized controlled trials. Medline, Web of Science, Scopus, and Cochrane Library were searched. Two reviewers blinded and independent found eight studies (a total of 618 patients with cancer). None of the studies achieved a “low” overall risk of bias. Four studies were included in meta-analysis for quality of life, and a significance standardized mean difference was found between groups from baseline of 14.62; 95% CI, 6.03-3.20, with a large effect size g=0.83; 95% CI, 0.48-1.18) in favor of

physical exercise program compared with usual care. Physical exercise at the onset of chemotherapy has shown promising effects on the prevention of CIPN, specially improving quality of life. However, the diagnosis of CIPN is not avoided with the proposed physical exercise programs in all patients; the severity of symptoms can be reduced. For that reason, looking to the evidence of the physiological potential of BFR plus physical exercise on other disorders, it is proposed analysing the effects of **PRESIONA** (**Study II**) to prevent CIPN in women with early breast cancer undergoing neoadjuvant chemotherapy. **PRESIONA** will be a physical therapist-led multimodal exercise program that uses BFR during low-load aerobic and strength exercises. Feasibility will be quantified and in the efficacy study, the main outcome will be EORTC QLQ-CIPN20. The innovative approach of this study could have a far-reaching impact on therapeutic options, and the physical therapist role could be essential in the oncology unit to improve quality of life in individuals with cancer and reduce side effects of cancer and its treatments.

Keywords: Drug therapy; Exercise; Neoplasms; Peripheral Nervous System Diseases; Quality of life; Rehabilitation.

RESUMEN

La neuropatía periférica inducida por la quimioterapia es una toxicidad limitante de dosis de muchos agentes de uso común en el tratamiento contra el cáncer. Se genera por daño axonal y del ganglio de la raíz dorsal, y es, por tanto, predominantemente una neuropatía sensorial que puede influir tanto en la supervivencia como en la calidad de vida. Los programas de ejercicio físico parecen ser factibles y eficaces para reducir los síntomas de la neuropatía inducida por quimioterapia. Sin embargo, de hecho, hasta ahora el tratamiento de la neuropatía inducida por quimioterapia sigue sin tener cura y carece de un sólido arsenal terapéutico tanto farmacológico como no farmacológico. Así, el impacto de la neuropatía inducida por quimioterapia ha llevado a investigadores y clínicos a cuestionarse qué dosis de ejercicio físico es más adecuada en pacientes con cáncer para su prevención. Esta Tesis Doctoral pretende contextualizar el estado del arte del ejercicio físico para prevenir la neuropatía inducida por quimioterapia en pacientes con cáncer (**Estudio I**) y proponer un programa de ejercicio físico combinado con restricción del flujo sanguíneo (RFS) con potencial para prevenir la neuropatía (PRESIONA) (**Estudio II**).

Para el **Estudio I**, se realizó una revisión sistemática con metaanálisis para analizar los efectos del ejercicio físico aplicado antes o durante la quimioterapia para prevenir o mejorar la neuropatía inducida por quimioterapia en ensayos aleatorizados y controlados. Se realizaron búsquedas en las bases de datos Medline, Web of Science, Scopus y Cochrane Library. Dos revisores cegados e independientes encontraron ocho estudios

(con un total de 618 pacientes con cáncer). Ninguno de los estudios alcanzó un riesgo general de sesgo "bajo". Se incluyeron cuatro estudios en el metaanálisis para la calidad de vida, y se encontró una diferencia de medias estandarizada significativa entre los grupos con respecto al valor inicial de 14,62; IC del 95%, 6,03-3,20, con un tamaño del efecto grande g=0,83; IC del 95%, 0,48-1,18) a favor del programa de ejercicio físico en comparación con la atención habitual. El ejercicio físico al inicio de la quimioterapia ha mostrado efectos prometedores en la prevención de la neuropatía periférica inducida por quimioterapia, especialmente mejorando la calidad de vida. Sin embargo, el diagnóstico de esta neuropatía periférica no se evita por completo con los programas de ejercicio físico propuestos; lo que se puede producir es una reducción de la gravedad de los síntomas. Por ello, atendiendo a la evidencia del potencial fisiológico de la RFS más ejercicio físico sobre otras patologías, se propone analizar los efectos de **PRESIONA** (**Estudio II**) para prevenir la neuropatía periférica inducida por quimioterapia en mujeres recién diagnosticadas con cáncer de mama tratadas con quimioterapia neoadyuvante, a través de un protocolo de un estudio aleatorizado y controlado. **PRESIONA** será un programa de ejercicio multimodal dirigido por un fisioterapeuta que utilizará RFS durante ejercicios aeróbicos y de fuerza de baja carga. Se cuantificará la tanto la viabilidad como la eficacia de **PRESIONA**. En el estudio de eficacia, el resultado principal será reportado por el cuestionario EORTC QLQ-CIPN20. El enfoque innovador de este estudio podría tener un impacto de gran alcance en las opciones terapéuticas, y el papel del

fisioterapeuta podría ser esencial en la unidad de oncología para mejorar la calidad de vida de las personas con cáncer y prevenir los efectos secundarios derivados del cáncer y sus tratamientos.

Palabras clave: Farmacoterapia; Ejercicio; Neoplasias; Enfermedades del sistema nervioso periférico; Calidad de vida; Rehabilitación.

INTRODUCTION

Cancer is listed as the new worldwide epidemic(1); nevertheless, increasing survival and quality of life in patients with cancer remains a challenge. One of the most promising advances in terms of treatment has been the implementation of systemic treatment, such as chemotherapy protocols(2), which typically consist of cyclically administering metal-based compounds. The aims of this therapy are to reduce tumor size, improve breast conservation rates, eliminate possible micrometastases, recognize poor responders to limit the toxicity of ineffective therapy(3), and produce a complete pathological response(4). However, despite being very effective for cancer, chemotherapy has a great impact on the peripheral nervous system, which is known as neurotoxicity(5).

DRUGS INDUCED PERIPHERAL NEUROTOXICITY

Chemotherapy-induced peripheral neuropathy or neurotoxicity (CIPN) represents a great challenge in the management of patients with cancer because it is one of the most disabling symptoms (6). CIPN can be induced by several cytotoxic drugs such as antitubulins (paclitaxel, docetaxel, ixabepilone, and vincristine), platinum analogues (cisplatin, carboplatin, and oxaliplatin), and the proteasome inhibitors bortezomib and thalidomide (7). It is estimated that up to 65% of patients develop

CIPN (8,9) and that CIPN is one of the main reasons for medical treatment discontinuation (10), therefore affecting survival (8,11,12). A reduction in neurotoxicity could improve quality of life due to the decrease in associated symptomatology and the increased survival caused by planned treatment compliance.

The clinical presentation is CIPN, which is a dose-limiting toxicity for many commonly used anticancer agents. In fact, CIPN can lead to dose reductions of cancer therapy(10), as it has been described above, which may influence survival and quality of life(13).

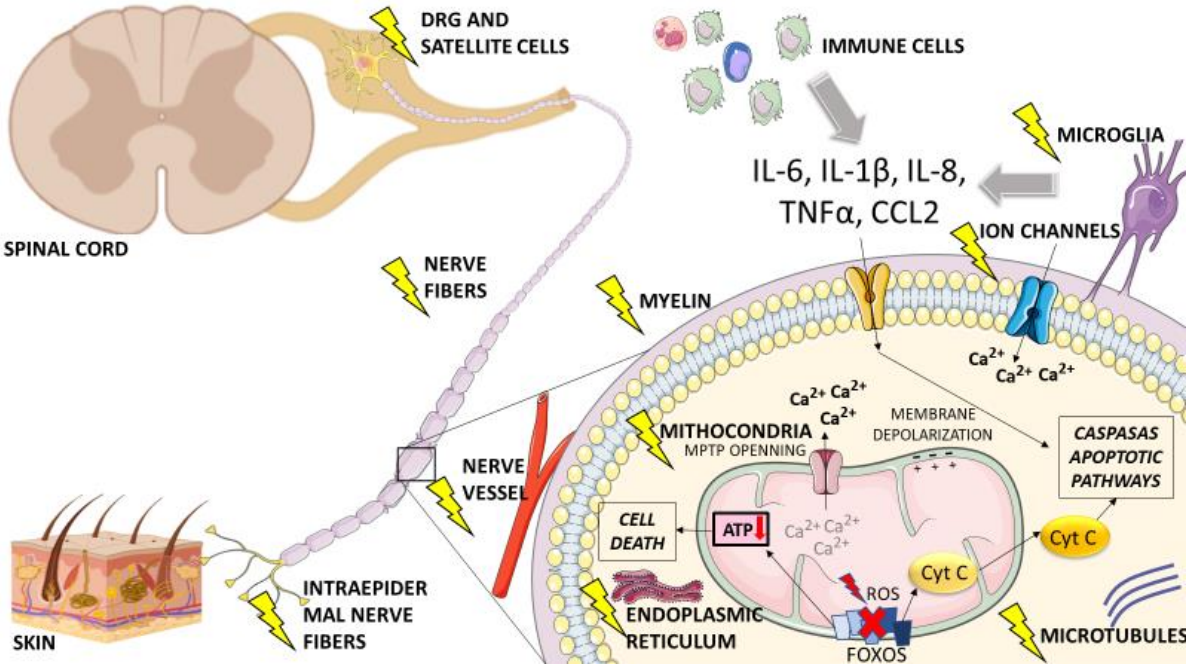
PHYSIOPATHOLOGY

CIPN is generated by axonal and dorsal root ganglion damage(14) and predominately is a sensory neuropathy rather than a motor one, but the intensity of dysfunction can also impair physical functions.

Regarding the toxicity of chemotherapy, current evidence shows that high levels of chemotherapeutic drug accumulation have been found in different areas of the peripheral nervous system (15), in the spinal cord and dorsal root ganglia as well as in its satellite cells (16). Chemotherapy also affects nerve fibres axons, causing

damage to the microtubules, myelin, ion channels and mitochondria (17). CIPN is initiated and progresses as a result of the deterioration of intraepidermal nerve fibres, leading to an innate activation of the immune system (17). There is a depolarization of the membrane and an alteration of calcium homeostasis in the mitochondria; consequently, the mitochondrial permeability transition pore opens and ATP synthesis is progressively blunted. Finally, cytochrome C is released into the cytoplasm, inducing apoptotic pathways (17–21). On the other hand, chemotherapeutic drugs head inflammatory-pathway activation and increased release of pro- and anti-inflammatory cytokines and chemokines (22), such as tumour necrosis factor alpha (TNFα), interleukin 1 beta (IL-1β), IL-6, IL-8, and chemokine C-C motif ligand 2. All these factors cause nociceptors and fibres sensitization, what it means neuropathy (22–26). In conclusion, different mechanisms affect many neural components and increase reactive oxygen species (ROS) and inflammatory mediators, which leads to a cytotoxic environment for neurons that induces neuropathic pain (Figure 1).

Figure 1. Representative image of the alterations produced by chemotherapy involved in the development of the CIPN. The lightning symbolizes where chemotherapy affects.



RISK FACTORS

Despite this widespread involvement, not all patients undergoing chemotherapy develop CIPN. The most important risk factor is the accumulation of chemotherapy doses (27), but CIPN is also associated with genetic susceptibility (28), age, smoking, obesity, sedentary lifestyle (29), co-occurrence of neuropathy (30), and chronic inflammation (31).

SYMPTOMS AND SIGNS

Symptomatology is largely subjective, and patients often experience numbness, tingling and pain in their fingers, affecting activities of daily living and manual dexterity (32). Moreover, CIPN negatively affects psychological wellbeing and sleep quality (33) and can have a significant impact on physical function in patients, thus increasing fall risks (34).

CIPN is a dose-limiting toxicity exerted on the peripheral nervous system. Symptoms are mainly sensory and usually include acral pain and paraesthesia, accompanied by allodynia and hyperalgesia (35) that appears in the hands and feet, including impaired perception of vibration sense and proprioception (36). The loss of sensitivity plus possible muscle weakness turn into moderate to severe balance problems, which might result in falls (37,38). Therefore, considering these symptoms and signs, it seems to be logical to include CIPN among factors involved in the deterioration of a patient's quality of life (13). This translates into an average $17,344 surcharge as a result of hospitalization and outpatient costs derived from CIPN (39). After taking everything into account, CIPN is an alarming process because drugs or complementary therapies (e.g., duloxetine, menthol-based creams) are not as effective as expected (19,40).

Traditionally, these symptoms and signs are usually used for diagnosis (41), although there are emerging tools to facilitate early detection of neurotoxicity, such as electrophysiological nerve conduction studies and quantitative sensory testing, to complete the diagnosis (42). Currently, more advances in early detection are still needed to improve its prevention.

CURRENT TREATMENTS STRATEGIES

One of the most commonly used therapeutic applications of physical exercise is to ameliorate CIPN (43,44). In recent years, supervised physical exercise programs have become a widely used tool for patients with cancer. Many of the health benefits of physical exercise are thought to be related to its short-term strengthening of the immune system and long-term anti-inflammatory effects (45,46), weight control (47) and improved control of endogenous sex hormone levels (48).

Physical exercise programs appear to be feasible and effective at reducing CIPN symptoms (43). However, in fact, so far CIPN treatment still no cure and lacks robust evidence both for pharmacological and non-pharmacological. Thus, the impact of CIPN in addition to the associated health costs (39) has led researchers and clinicians to question which dose of physical exercise is more suitable in patients with cancer for prevention of CIPN.

CURRENT PREVENTIVE STRATEGIES

CIPN is influenced by multiple elements that affect the patient's biopsychosocial sphere; therefore, multiple studies examine prevention from different perspectives. Despite the evaluation of many therapies, such as drugs, vitamins, minerals, and herbs traditionally used for neuropathic pain, no study has demonstrated efficacy in CIPN prevention (49). Some nonpharmacological therapies have achieved reduced CIPN incidence during chemotherapy. Among them, nurse-led quality of life care programmes have been shown to modulate the perception of pain from CIPN in oncological patients (50). Other researchers have tried to decrease chemotherapy pharmacokinetics and penetration into intraepidermal nerve fibres using a regional blood flow restriction (BFR) in the hands and feet. This regional BFR may be produced by cryotherapy, for example, using frozen gloves and socks during chemotherapy (51); this method has reduced some neuropathy symptoms, potentially resulting in a better quality of life. Additionally, frozen gloves could reduce the risk of a dose-limiting event due to CIPN, increasing the proportion of patients completing their planned chemotherapy, but it is a painful and poorly tolerated treatment (52,53). Furthermore, compression therapy using tight surgical gloves can produce BFR due to a decrease in microvascular flow to the fingertips (54). It has been shown that this treatment is safe and effective and reduces CIPN incidence,

but it does not completely prevent it. Despite being a promising treatment, trials have only evaluated four chemotherapy cycles, and no long-term efficacy evaluation has been conducted. For these reasons, new therapeutic strategies are starting to be considered, such as physical exercise.

PHYSICAL EXERCISE AS PREVENTIVE TOOL

The powerful effects of physical exercise and activity are increasingly evident in worldwide populations (55); its physical, mental and social benefits justify its success against systemic processes such as cancer (56). In recent decades, physical exercise in patients with cancer has shifted from health to a therapeutic focus (57). A recognized advance has been the initiation of physical exercise programs in patients who undergo active treatments (58–60). Some researchers have shown that patients who are physically active following a diagnosis of cancer have a lower risk of cancer recurrence and mortality with less severe side effects, including CIPN (61,62). Therefore, due to improvements in the immune system and chemotherapy delivery, physical exercise is considered an important adjunct therapy in the management of cancer itself (63). For that reason, oncologists should encourage their patients (if there is no contraindication) to remain physically active and be included in physical exercise program (64) which must be tailored though

prescriptions for frequency, intensity, time and type (FITT) following the guideline recommendations (65).

Among the proposed preventive strategies, physical exercise has a robust neuroprotective effect in preclinical studies, and it also helps repair nerve damage after CIPN, preserves myelin fibres and prevents hyperalgesia (66). It has been described that performing physical exercise while undergoing chemotherapy does not worsen CIPN symptoms. Physical exercise decreases CIPN-related risks (67) and enhances balance and strength (68), resulting in better quality of life (69). It has been demonstrated that patients who were exercising more prior to, during and following neurotoxic chemotherapy suffer less CIPN (49), but the results are not robust enough to implement this strategy in healthcare systems.

Physical exercise during chemotherapy has shown neuroprotective effects against CIPN and has a level of evidence and grade of recommendation of IIC (70). Evidence indicating the most successful physical exercise intervention to prevent CIPN remains scarce (71,72) due to heterogeneity of studies. The intensities and load of physical exercise usually used in prevention studies during chemotherapy are moderate to high (68,73,74). These features potentially represent a handicap in patients with cancer given the barriers of perceived exertion effort in this population (75). Adherence rates to high-intensity programs tend to be higher among active

people (76), and many patients are sedentary and even reduce their physical activity at the time of diagnosis (77,78).

BLOW FLOW RESTRICTION

In the past few years, a combination of physical exercise and BFR has been used in various clinical populations pursuing different objectives as mentioned below (79,80). This strategy consists of partially restricting arterial inflow and fully restricting venous outflow in working musculature during exercise (81).

According to previous evidence, the effects of physical exercise could be complemented with the effects of the blood flow restriction (BFR) method. In this type of training, a limitation of the arterial supply to the muscles of the extremities is generated while individuals are exercising (81). The performance of this combination at low intensities [40-50% maximum volume of oxygen (VO_2max) or 20-40% repetition maximum (RM)] generates extra physiological and metabolic stimuli that produce cardiorespiratory and neuromuscular adaptations (82,83) without causing muscle damage (84). This method promotes a marked elevation of hemodynamic variables and a greater demand for energy during and after exercise (83) as well as acute activation of the immune system (84) and an improvement in the antioxidant barrier (85–87). The justification for the innovative approach of physical exercise and BFR

in patients with cancer involves a systemic view that includes how physical exercise and BFR may mediate oxidative stress (88–90), immunity (91,92) and fibrinolytic system response (93). These mechanisms do not occur in isolation, and the neuromusculoskeletal system may be enhanced (90,94,95) to protect against chemotherapy neurotoxicity. In addition, the reported values of perceived exertion and pain in BFR training are not necessarily high compared to those in an equivalent form of higher intensity exercise without BFR (96). This method has no remarkable adverse effects (97).

Regarding resistance exercise in healthy individuals, low-load physical exercise with BFR has similar effects on maximal muscular strength and hypertrophy than high-load strength exercise without BFR, irrespective of the large discrepancy in external loading intensity (BFR: 20%-30% 1RM vs high-load: 60%-90% 1RM) (98,99). Low-load resistance exercise with BFR produces a metabolic stimulus due to hypoxia and metabolic stress (H +, Pi, lactate accumulation). This metabolic stimulus is known to mediate the activation of pro-inflammatory cytokines and cells of the immune system (IL-6, macrophages, and neutrophils). Taken collectively, these anabolic stimuli could help explain the effectiveness of such methods in the absence of high mechanical forces and muscle damage (100). Similar results have been found in muscular strength and hypertrophy in the elderly who used low-load resistance

exercises (20-30% 1RM) (101,102) or aerobic-type exercise (45% of heart rate reserve) to BFR (103). This finding is of vital importance in this population is often unable to exercise at high intensities. During rehabilitation, especially in the initial postoperative phases, low-load resistance exercise with BFR is more comfortable than high-load, although the perceived effort is the same (104). In addition, joint stress and effusion are decreased as well as pain, leading to greater overall improvements in physical function (105,106). The mechanisms of pain reduction with this method are not yet understood. On the one hand, muscle strength gain is associated with pain relief (107). On the other hand, pain from cuff pressure and ischemia, in addition to exercise-induced muscle pain itself, may contribute to modulated nociceptive response (108,109), as consequence, these findings make this method an alternative to high-load resistance exercise during rehabilitation (96). Finally, BFR in athletes improves performance, particularly considering the relatively short duration of the intervention (110). In view of the benefits, it is possible that the improvements obtained from physical exercise - BFR can be obtained from conventional training but with shorter interventions. Regarding BFR safety, the acute effect of BFR during training has not been related to negative coagulant responses; however, there is some concerns in exercising with BFR in individuals with established cardiovascular disease. To some extent, this method has been restricted

to this population, since it increases the pressor reflex and therefore the cardiac autonomic response (111). However, a review has found hemodynamic changes within normal ranges of being considered theoretically safe for cardiac patients (112) and some clinical trials have performed interventions with BFR in the cardiac patients considering it as a safe tool (113), without reporting considerable adverse effects (88,113). Despite this, the results should be interpreted with caution and await trials with long-term results. Only minor numbers of adverse effects have been reported with low incidence rates, such as venous thrombus (0.05%), pulmonary embolism (0.01%) and rhabdomyolysis (0.01%) (114). Patients with cancer who have received medical clearance may benefit from physical exercise - BFR, but no clinical trials have been performed in this population. In 2019, Miguel S. Conceição and Carlos Ugrinowitsch claimed that future studies are needed to ensure the safety of BFR training in patients with chronic diseases diagnosed with muscle wasting (e.g. patients with cancer) (115). In this way, a multimodal prehabilitation program (four weeks), was comprised of blood flow restriction exercise 5 to 6 times per week and a daily sports nutrition supplement containing l-citrulline, creatine monohydrate, and whey protein. The authors found both feasible and effective in improving lean mass and physical function in abdominal cancer patients prior to surgery (116). To our

knowledge, there is no previous experience in women with breast cancer to prevent neurotoxicity.

LITERATURE GAPS

In 2023, they have called for prevention to be a priority. Thus, the European Society for Medical Oncology, a reference institution in Europe (https://www.esmo.org/), has just highlighted the need to anticipate and prevent sequelae of the disease and its treatments.

Regarding CIPN, recently in 2019, the National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee concluded that 'CIPN is a priority area of translational research in cancer care' (117). Therefore, many treatments are still being tested without consensus (19), and the results have provided new recommendations to be explored, including methods for the prevention of CIPN (118). A reduction in neurotoxicity might improve quality of life due to not only the decrease in associated symptoms (53) but also the longer survival derived from compliance with the planned treatment (52).

The scientific community has exhibited a growing interest in the prevention of CIPN due to the large research gaps. First, CIPN is a persistent problem that results in

chronic condition (9). According to the best available evidence, no definitive therapy has been found. In fact, the importance of CIPN prevention has led to the publication of recommendations by experts (118), facilitating the development of new effective and safe therapies without side effects.

To our knowledge, there are few reviews about the effects of physical exercise programs on CIPN prevention. One analyzed pharmacological and nonpharmacological therapies and revealed that the level of evidence and grade of recommendation for exercise is IIC (40); that is, insufficient evidence for efficacy does not outweigh the risk or disadvantages. This statement was justified by a single but well-designed randomized controlled trial (RCT) (although with low power and inconsistent findings). Another narrative review focused on different options for the prevention and treatment of CIPN suggested that exercise may be used in an attempt to avoid occurrences of CIPN (119). However, this narrative review utilized a basic methodology whose results were inconclusive and called for additional supporting data. Recently, another review focused mainly on behavior and physical exercise (120). Despite the identified evidence related to existing behavioral and exercise interventions for preventing or managing symptoms of CIPN, Tanay and colleagues (120) were interested in understanding the psychological mechanisms of action that may have influenced an individual to perform exercise to manage CIPN. Among

potential records under review, there is one registration related to physical activity and exercise to prevent CIPN in a very early review phase, and it is not yet published (121). Although it lacks a meta-analysis, its objective is largely focused on falls and impaired balance, although CIPN is a more complex syndrome, as described above. Furthermore, in 2019, A Hammond and colleagues (122) indicated that future research needs to identify the specifics of exercise prescriptions (intensity, frequency, duration, and type) to provide the most benefit for the prevention of CIPN. Thus, there are still some gaps to be addressed. More evidence is needed to justify the prevention or reduction of CIPN incidence as a primary endpoint (123) and to clarify the impact of physical exercise programs on CIPN and related outcomes (124).

OBJECTIVES

The overall aim of this doctoral thesis is to address CIPN in a preventive way through physical exercise with blood flow restriction.

SPECIFIES OBJECTIVES

Section 1: Contextualise the state-of-the-art of physical exercise to prevent CIPN in patients with cancer.

* Study I:

- Synthesize studies that perform physical exercise during chemotherapy.
- Identify the specific parameters of physical exercise programs that provide the most beneficial prevention of CIPN in patients with cancer.
- Analyze the most relevant outcomes related to CIPN.

Section 2: Propose a physical exercise program with the capacity to prevent neuropathy (PRESIONA).

* Study II:

- Elaborate a protocol of evaluation of CIPN.
- Summarize the parameters of physical exercise + BFR proposed.
- Propose an efficacy analysis, measuring outcomes both short and long-term results, as well as a feasibility analysis.

SECTION I

Contextualise the state-of-the-art of physical exercise to prevent CIPN in patients with cancer

Study I

Can Physical Exercise Prevent Chemotherapy-Induced Peripheral Neuropathy in Patients with Cancer? A Systematic Review and Meta-analysis

AIMS

In view of works already published, this systematic review with a meta-analysis that exclusively analyzes physical exercise programs in patients with cancer undergoing chemotherapy with special emphasis on clarifying the key points of physical exercise programs to prevent CIPN. For this reason, the aim of this review is a) to synthesize studies that perform physical exercise during chemotherapy; b) to identify the specific parameters of physical exercise programs that provide the most beneficial prevention of CIPN in patients with cancer; and c) to analyze the most relevant outcomes related to CIPN.

METHODS AND RESULTS

Protocol and registration

To reduce duplication of effort and publication bias (125,126), this study was registered and accepted in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) on 20th November 2020 and can be accessed at https://www.crd.york.ac.uk/prospero/ with the following registration code: CRD42020214356. PROSPERO registered was done when preliminary searches and piloting of the study selection process were performed. This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines (127). The specific question posed for this review was: What kind of physical exercise program has the greatest effect on the prevention of CIPN in patients with cancer?

ELIGIBILITY CRITERIA

For this review, only published studies until 20th December 2020 were considered. No restrictions were placed on year, but publications were limited by English or Spanish language. Based on the PICOS strategy (128), RCTs in which physical exercise was applied before or during chemotherapy to prevent or ameliorate CIPN were included (Table 1). Prevention of CIPN has been stablished as any therapy administrated prior to the start of chemotherapy (primary prevention) or the appearance of moderate to severe CIPN during medical treatment in order to prevent worsening (secondary prevention) (118).

Table 1. Research strategy using PICOS strategy

Research idea	PICOS					Research question
	Participants	**I**ntervention	**C**omparation	**O**utcomes	**S**tudy design	
Physical exercise in patients undergoing chemotherapy could prevent CIPN	Patients with cancer undergoing chemotherapy	Any kind of exercise or physical activity modalities	No restriction was applied	CIPN development	Randomized controlled trials (RCT)	What kind of physical exercise program has the greatest effect on prevention CIPN?

INFORMATION SOURCES

A detailed literature search was carried out in Medline [via PubMed searcher] (Table 2), Scopus, Web of Science, and Cochrane Library. The literature search was conducted from 20th October to 1st December 2020. Furthermore, an automatic alert notification for new publications was created in all databases. Apart from this, reference lists of retrieved reports were also manually searched for additional references.

Table 2. Search strategy in MEDLINE database

PICOS Components of Search Strategy	
P	(Chemotherapy[Mesh] OR Chemotherap*[All fields] OR Chemotherapy Adjuvant[Mesh terms] OR Chemotherapy Adjuvant[All fields] OR Drug Therapy Adjuvant[tiab] OR Neoadjuvant Therapy[Mesh terms] OR Neoadjuvant Therap*[All fields] OR Treatment* Neoadjuvant[tiab])
I	(Exercise[Mesh] OR exercise*[All fields] OR Activit* Physical[tiab] OR Exercise* Physical[tiab] OR Exercise* Acute[tiab] OR Exercise* Isometric[tiab] OR Exercise* Aerobic[tiab] OR Exercise Training[tiab] OR exercise movement techniques[tiab] OR Breathing exercise[tiab] OR Dance therapy[tiab] OR Tai Ji[tiab] OR Yoga[tiab] OR Exercise therapy[Mesh] OR exercise therapy[tiab] OR Endurance training[tiab] OR Motion therapy continuous passive[tiab] OR muscle stretching exercise[tiab] OR Plyometric exercise[tiab] OR Resistance training[tiab])
C	-
O	(Peripheral Nervous System Diseases[Mesh terms] OR Peripheral Nervous System Disease*[All fields] OR Disease* PNS[tiab] OR Neuropath* Peripheral [tiab] OR Nerve Disease* Peripheral[tiab] OR Peripheral Nervous System Disorder*[tiab] OR Small Fiber Neuropathy[Mesh] OR Neuropath* Small Fiber[All fields] OR Polyneuropathies[Mesh] OR Polyneuropath*[All fields] OR Polyneuropath* Motor[tiab] OR Neurotoxicity Syndromes[Mesh] OR Neurotoxicity syndrome*[all fields] OR Neurotoxin Disorder*[tiab] OR Neurotoxic disorder*[tiab] OR Neurotoxin disease*[tiab] OR Chemotherapy induced peripheral neuropath*[tiab] OR CIPN[tiab] OR Chemotherapy Induced Polyneuropath*[tiab] OR Chemotherapy induced peripheral neurotoxicit*[tiab] OR Chemotherapy Induced Neuropathic Pain[tiab] OR Platinum induced peripheral neurotoxicit*[tiab] OR Bortezomib induced peripheral neuropath*[tiab] OR BIPN[tiab] OR Taxane induced peripheral neurotoxicit*[tiab] OR TIPN[tiab] OR Cancer treatment induced neurotoxic*[tiab] OR Platinum drugs induced peripheral neurotoxicit*[tiab] OR chemotherapy induced painful peripheral neuropath*[tiab] OR Bortezomib Induced Neuropathic Pain[tiab] OR Chemotherapy induced neuropath*[tiab] OR platinum induced peripheral neuropath*[tiab] OR neuropathy induced by bortezomib[tiab] OR Bortezomib induced polyneuropath*[tiab] OR Taxane induced neurotoxic*[tiab] OR bortezomib induced neurotoxic*[tiab] OR taxane induced neuropath*[tiab] OR taxane induced peripheral neuropath*[tiab] OR bortezomib related chemoneuropathy patients[tiab] OR chemoneuropath*[tiab] OR Therapy related peripheral neuropath*[tiab] OR cancer neuropath*[tiab])
S	(Randomized controlled clinical trial*[tiab] OR randomized controlled clinical trial*[tiab] OR randomized controlled trial*[Publication Type] OR randomized controlled trial*[Publication Type] OR randomized controlled trials as topic[MeSH Terms] OR randomized controlled trial*[All Fields] OR randomized controlled trial*[All Fields] OR clinical controlled trial*[tiab] OR controlled clinical trial*[tiab] OR clinical trial*[tiab] OR random allocation[tiab] OR randomly allocated[tiab] OR allocated randomly[tiab])

SELECTION OF SOURCES OF EVIDENCE

A literature search was conducted by a single reviewer (MLG) using relevant subject headings, keywords and modifications made according to the databases searched; modifications were made to fit each database. All articles were retrieved and exported to Rayyan where a single reviewer removed duplicates in Rayyan (129). Then, two independent and blinded reviewers (MLG and ÁGS) identified and selected titles and abstracts according to the inclusion criteria. All articles identified in the first screening process were included in the following one, in which selected articles were thoroughly read and screened for the inclusion criteria by the same reviewers. Articles considered eligible after full-text view by mutual consent were included in the final analysis. Reasons for exclusion were recorded. In case of disagreement, a third external researcher (NGC) was consulted to make the final decision, and the last researcher calculated the percentage of agreement.

SYNTHESIS OF RESULTS

The following data will be extracted from each article by two independent and blinded reviewers review (MLG and NGC): (1) general study details: Title, authors, source, and year of publication; (2) study eligibility: type of study, participants characteristics including, number of participants, age, gender, diagnosis, type of cancer treatment,

stage of cancer, methods including design/allocation, blinding, sampling, loss to follow-up, and adherence rates, intervention characteristics including type of physical exercise, types of outcome measures including self-reported outcomes, objective outcomes; (3) study details: details of intervention including, frequency, intensity, time and type, program length, and results of the study. The data extraction was documented in a Microsoft Excel spreadsheet. In addition, a narrative synthesis was carried out according to FITT prescription(65).

RISK OF BIAS AND QUALITY OF DATABASES

Since one of the inclusion criteria was RCT design, each article was critically appraised using the Cochrane Risk of Bias tool RoB 2 (130) by two blinded reviewers (MLG and PPM). The quality of the chosen databases was also determined by sensitivity/precision analysis.

DATA ANALYSES

Only those studies that measured quality of life, presented all available data, and used usual care as comparator, were included in our meta-analysis. In those studies, in which the data were not present in the manuscript, the authors were contacted.

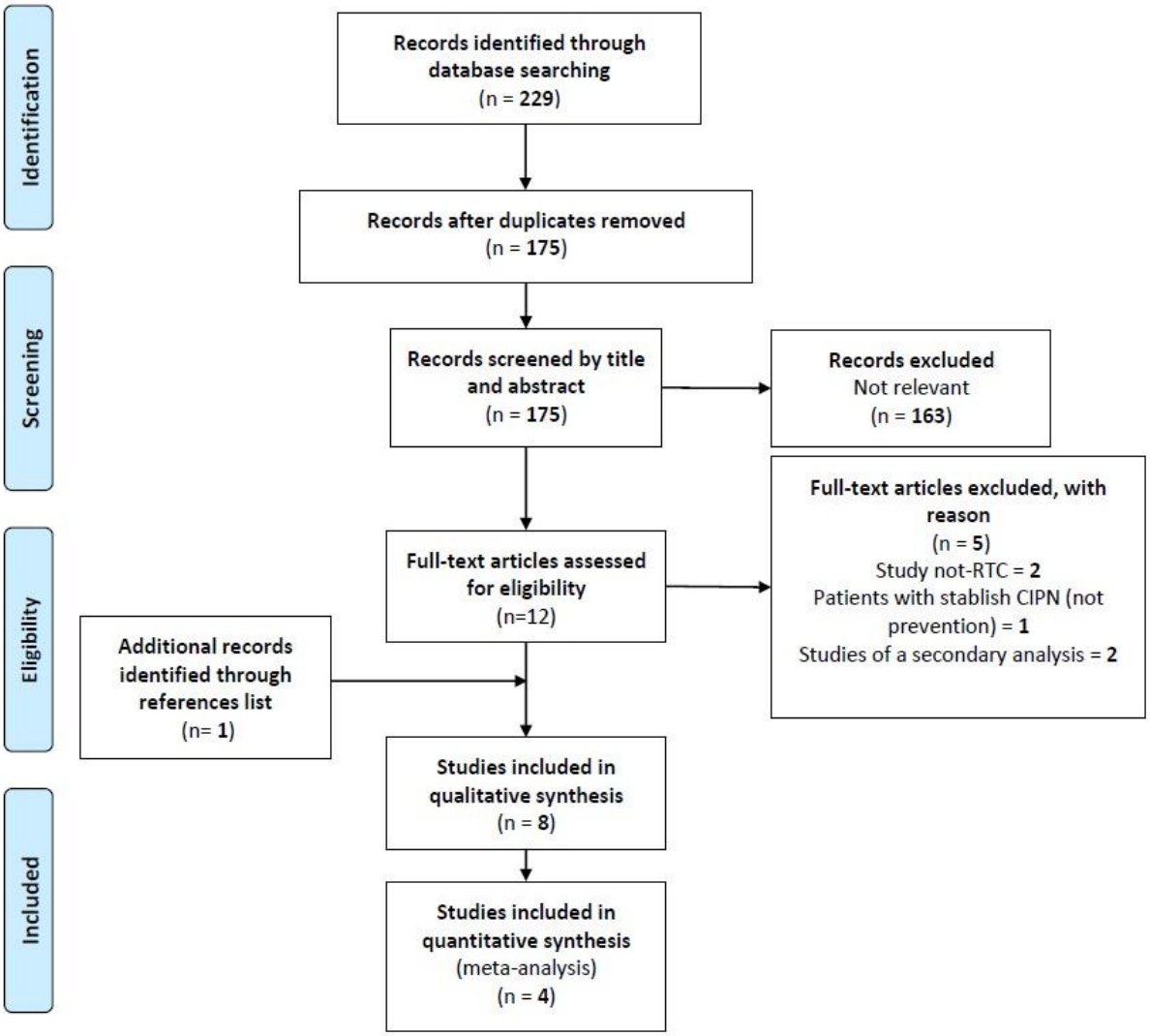
The data were extracted from the tables, the text of the article, or the images that were digitized using the online tool WebPlotDigitizer v. 4.4 (Pacifica, California, USA)(131). All studies selected were combined using the random effects model of the DerSimonian and Laird method, which takes into account variations within and between studies. In addition, the Hartung-Knapp adjustment was used considering the uncertainty in the estimation of the variance among the studies of the random effect method (132). Forest plots were used to visualize individual study summaries and pooled estimates. To assess heterogeneity among studies, the Cochran Q statistics were used along with the I2 value. A mean difference was calculated for each of the original studies, and a two-sided p-value $<.05$ was considered statistically significant. Finally, a sensitivity analysis was carried out to study the consistency of the results. Additionally, Hegdes' g effect size of each study was calculated in the meta-analysis. Stata software was used to carry out quantitative combination of the studies.

RESULTS

The initial searches returned 229 studies, 54 of which were removed during duplicate screening. The title and abstract screening of the remaining 175 studies resulted in

12 studies meeting the inclusion criteria. Five of these studies were subsequently excluded at the full text phase. One study was added from the reference list, and none were found with automatic alerts. A total of eight studies met the inclusion criteria and were assessed. Interrater agreement in the selection of studies was 48.1% (133). After discussion, the reviewers reached consensus (100%). Details of the literature search and study selection are shown in Figure 1.

Figure 1. Flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.



CHARACTERISTICS

A total of 618 patients were included in the narrative synthesis (Table 3). Considering all eight studies, 318 patients were allocated to the intervention group (IG), and 300 of them were allocated to control group (CG). The sample size of the included studies

ranged from 28 to 355 patients, of whom 78% were female, and the average age was 56.63 ± 23.17 years in IG and 57.53 ± 8.56 years in CG. The most predominant type of cancer was breast (17%)(134–137), followed by lymphoma (13%) (137,138), colorectal (8%)(68,137), lung (7%)(137,139), gastrointestinal cancer (4.5%) (140) and others not reported (4%). With respect to treatments, all of them were potentially neurotoxic(9). The most common was the administration of docetaxel or paclitaxel in cycles distributed every one, two, three or four weeks(134–137). Additionally, other regimens used were platinum derivatives(137,139) and FOLXOS therapy(68). All patients were chemotherapy-naïve, except in one(68), where up to 60% of patients had received cycles of chemotherapy prior to the study. In another study the prior use of chemotherapy was not reported(139). Most studies reported that the time of the physical exercise program coincided with chemotherapy treatment.

Table 3. Characteristics of eight randomized controlled trials (RCTs) regarding physical exercise for outcomes in chemotherapy-induced peripheral neuropathy (CIPN).

1st Author (year)	Groups (numbers of participants)	Type of cancer (stage)	Program duration (frequency)	Intensity	Measured time points	Measured tools	Results	Adherence	Adverse effects
Multimodal physical exercise: endurance, resistance, and balance									
Bland (2019)	IE: immediate physical exercise during chemotherapy (n=15) DE: delayed exercise after chemotherapy (n=16)	BC (I-III)	8-12 weeks (supervised 3 days per week and after 3 weeks 2 days per week of home-based)	Endurance: 50-75% of HRR Resistance: 50-65 % of RM	Baseline Mid-chemotherapy After chemotherapy Follow-up	Quality of life (EORTC QLQ-C30) Neurotoxicity (EORTC QLQ-CIPN20) Vibration senses (present or absent)	**Quality of life** *Intergroup:* p = .05 (after chemotherapy, IE>DE, $g = 1.57^{\#}$) p > .05 (follow-up) *Intragroup*: P < .01 (baseline to follow-up, both groups combined increase. **Neurotoxicity** *Intergroup*:	IE: 80.66%; DE 89.33% †	Reported (follow-up cancer recurrence in IE n=1)

								p > .05 (any time points, IE vs DE) **Vibration sense** *Intergroup*: p < .01 (at mid-chemotherapy, IE > DE)		
Streckmann (2014)	IG (n=30) CG: Usual care (n=31)	Lymphoma (any stage)	36 weeks (twice per week)	Endurance: 60-80% HR max Resistance: Maximal force or theraband in inpatients	Baseline Twice during chemotherapy (12 and 24 weeks) After intervention (36 weeks)	Quality of life (EORTC QLQ-C30) Vibration sense Sway area on static and dynamic surface	**Quality of life** *Intergroup*: p = .03 (at 12 weeks, IG > CG, g = .80[#]) p > .05 (after intervention) *Intragroup*: p = .03 (baseline to after intervention, IG increase) p > .05 (CG) **Vibration sense** *Intergroup over time:* p = .07 (IG > CG, after	65 %	Reported (none)

		intervention average incidence of PNP) p < .001 (after IG > CG reduction of PNP once develop) p = .002 (after, IG reduction PNP>CG) **Sway area static surface** *Intergroup:* P = .035 (after intervention, IG > CG) ***Sway area dynamic surface*** *Intergroup:* P = .007 (after intervention, IG > CG)

Vollmers (2018)	IG (n=17) CG: Usual care (n=19)	BC (not reported)	18 weeks (twice per week)	13–15 on the Borg Scale	Baseline After intervention Follow up (6 weeks)	Quality of life (EORTC QLQ-C30) Balance (Fullerton Advanced Balance Scale) Sway area (monopedal and bipedal stance)	**Quality of life** *Intergroup*: p > .05 **Balance** *Intergroup:* *p = .004 (after intervention, IG > CG).* *Intragroup:* *p < .001 (after intervention, IG increase, CG decrease)* **Sway area monopedal** *Intergroup*: p < .001 (after intervention, IG > CG) p < .01 (follow up, IG > CG) **Sway area bipedal** *Intergroup*:	Not reported	Not reported

								p = .039 (after intervention, IG > CG)		
Zimmer (2018)	IG (n=17) CG: Usual care (n=13)	CRC (any stage)	8 weeks (twice per week)	Endurance: 60-70% HR max Resistance: 60-80% of H1rm	Baseline After intervention Follow up (4 weeks)	Quality of life (TOI of FACT/GOG-NTX) Balance (GGT-Reha)	**Quality of life** *Intergroup*: p = .028 (after, IG>CG, *g* = .70[#]) p = .031 (follow-up, IG>CG) *Intragroup time effects*: p = .077 (baseline to after, IG decrease) p = .037 (baseline to follow-up, CG decrease) **Balance** *Intergroup:* *p > .05 (over time)*	80%	Reported (IG death n=2)	
Concurrent physical exercise: endurance and resistance										

Henke (2014)	IG concurrent training + breathing exercise (n=18) CG: Usual care (n=11)	Inoperable lung cancer (III-IV)	During three cycles of chemotherapy (endurance training and breathing techniques 5 sessions per week, strength once per week)	Endurance: 55-70 % HRR Resistance: 50% of maximal capacity.	Baseline After intervention	Quality of life (EORTC QLQ-C30)	**Quality of life** *Intergroup:* $p > .05$ (after intervention, $g = .46^{\#}$) *Intragroup:* $p > .05$ (after intervention, in both groups)	Not reported	Reported (not related to the program death n=6)
Kleckner (2018)	IG (n=170) CG: Usual care (n=185)	BC, lymphoma, CRC and lung cancer (any stage)	6 weeks (daily)	Endurance: 60–85% HRR Resistance: 3-5 rated perceived exertion scale	Baseline After intervention	Numbness and tingling (VAS) Hot and coldness (VAS)	**Numbness and tingling** *Intergroup:* $p = .061$ (after intervention, IG > CG, $d = .42$) *Intragroup:* $p = .027$ (IG + .38 points) $p = .003$ (CG + .58 points) **Hot and coldness** *Intergroup:*	77% for resistance proposals	Reported (lymphopenia, neutropenia, multiorgan failure n=5)

							p = .045 (after intervention, IG > CG, *d* = .46) *Intragroup:* p = .022 (after intervention, IG + .38 points) p < .0001 (after intervention, CG +.77 points)		
Other modalities									
Hammond (2020)	IG (n=22) home-based nerve gliding exercises CG: Usual care (n=26)	BC (I-III)	Until disappear	symptoms - (3 times daily)	Baseline Mid-chemotherapy Post-chemotherapy Follow-up (3 and 6 months)	Pain (VAS) Vibration sense (amplitudes µm/s)	**Pain** *Intergroup:* p = .053 (IG less pain than CG) *Intragroup:* p = .002 (IG less pain over time, OR .85) **Vibration sense**	Not reported	Not reported

								Intergroup: p > .05 (any time points)		
Stuecher (2019)	IG (n=13) home-based walking exercise CG: Usual care (n=15)	Gastroint estinal cancer (III–IV)	12 weeks (until complete 150 minutes per week)	Endurance: 46 to 63% of VO2peak	Baseline Mid-chemotherapy (4-6 weeks) After intervention	Functional status (SPPB) Sway area (bipedal static surface)	**SPPB** *Intergroup:* p > .05 (any time points) *Intragroup:* p < .05 (mid-chemo to baseline, CG decrease) **Sway area** *Intergroup:* *p = .001 (mid-chemo, IG > CG, d = .59†)* *p = .003 (after intervention, IG > CG, d = .95†)*	81.3%	Reported (not related to the program, hospitalization due to infection or severe fatigue n=3)

Abbreviations: BC: breast cancer; CG: control group; CRC: colorectal cancer; H1rm: hypothetic one-repetition maximum; HR: Heart rate; HRR: heart rate reserve; OR: Odds ratio; RM: repetition maximum; VO2 max: maximal oxygen consumption; †: indirectly calculated; #: effect size reported from meta-analysis of quality of life versus usual care.

COMPARATOR

Seven studies compared IG versus CG (68,134,136–140), and only one conducted superiority study with physical exercise interventions in all arms (135).

Physical exercise parameters according to FITT prescription (65).

FREQUENCY

Among all eight studies, four studies were committed to exercising twice (68,134,138), three (135), five (139) sessions per week or daily (136,137). Other authors not specified (140).

INTENSITY

The most commonly used intensity in endurance proposal was moderate in five studies (134,135,137–139); follow by low-to moderate intensity (68,140) or not specified(136). Intensity during resistance proposal was moderate (68,134,135,137,138) or not reported (134).

TIME

The duration of physical exercise program was six (137), eight (68,135), 12 (135,140), 18 (134) or 3642 weeks. Others not specified (136,139).

There is variability in the total number of sessions used 16 (68), 36 (134), 42 (137), 60 (135) and 72 (138). Another study reported 1800 minutes of walking throughout the program (140) or not specified (136,139).

The total session time lasted 15 (136), 20-50 (140), 60 minutes (68,137,138), or not specified (134,135,139). In each session, the time of endurance exercise was ten minutes in two studies (68,139). Other reported from 10 up to 50 minutes (135,138,140) or not specified (134,137).

TYPE

Four studies used the multimodal approach in their intervention (68,134,135,138), which included proposals of endurance, resistance and balance, two of them also hand and foot specific exercises (135) or coordination practice (68) were performed. Two studies used a concurrent physical exercise approach that only included endurance and resistance proposals (137,139). Other physical exercises included nerve gliding exercises (136) and a walking program (140).

The sessions were as follows: supervised (68,134,138,139), home-based (136,137,140) or a mix between supervised and home-based (135).

PROGRESSION

Linear progression in each of the components was used in two studies (137,140). While other two studies used non-linear- based on symptoms and the HR resting (135) or based on Borg dyspnea scale (139) was performed as endurance physical exercise progression.

ADHERENCE

The intervention with lower average adherence was in patients with lymphoma (65%) (138). The majority of studies obtained at least 80% adherence (68,135,140). However, there was a decrease in adherence when resistance proposals were examined, 77% (137). Three studies not specified (134,136,139).

ADVERSE EFFECTS

Some adverse effects were found, such as cancer recurrence(135), death(68,139), lymphopenia, neutropenia and multiorgan failure(137), hospitalization due to infection and severe fatigue(140). None of them were directly related to the intervention. Two studies not specified any adverse effects(134,136).

NEUROTOXICITY

Zimmer and colleagues(68) used the subscale of Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-NTX) and found an intergroup significant difference in favor of IG after intervention (p=.002) and at follow-up (p=.015). Additionally, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale (EORCT-CIPN20) was measured in two studies, but no intergroup significant difference was found (134,135).

PAIN IN CIPN

Two studies used the visual analog scale (VAS). Kleckner and colleagues(137) found an intergroup significant differences in favor of IG on hot and coldness symptoms (p=.045, d=.46, 95% CI .01, .91) after intervention. Hammond and colleagues (136) demonstrated a relevant clinical decrease in pain scores in favor of IG at the end of chemotherapy, although there was no intergroup significant difference.

VIBRATION SENSITIVITY

Bland and colleagues (135) studied the percentages of participants who presented vibration impairments, and there was an intergroup significant difference in favor of the immediate exercise group ($p < .01$) at middle chemotherapy. In another study, a tuning fork with a graduating scale from 0 (no sensitivity) to 8 (highest sensitivity) was used, and the average incidence of CIPN was registered. There was an intergroup significant difference in favor of IG among symptoms dismissed ($P < .001$, 87.5% in IG vs 0% in CG) and the number of patients suffering impaired vibration ($P = .002$), both after intervention (138). Other study used a vibration sensory analyzer that delivered random amplitudes while asking patients whether they felt vibration or not and did not find intergroup differences at any time point (136).

BALANCE

Vollmers and colleagues used the Fullerton Advances Balance Scale and found an intergroup significant difference in favor of IG after intervention ($p = .004$) (134). Stuecher and colleagues (140) measured balance in three static standing positions, and their results did not show intergroup significant differences at any time point. Another study also measured dynamic balance, although no intergroup difference was found (68).

SWAY AREA

Vollmers and colleagues(134) found an intergroup significant difference in favor of IG that showed a smaller sway area in monopedal stance after intervention (p< .001) and at follow-up (p< .01) in both feet. Sway area in bipedal stance also showed an intergroup significant difference in favor of IG after intervention (p= .039). Stuecher and colleagues (140) measured sway area on a static surface while patients stood bipodal and demonstrated an intergroup significant difference in favor of IG during middle chemotherapy (p= .001, d= .59, 95% CI -.10, 1.26) and after intervention (p =.003, d= .95, 95% CI .19, 1.67). Finally, Streckmann and colleagues (138) used static and dynamic surfaces to measure sway area on monopedal and bipedal stances and found an intergroup significant difference in favor of IG on static surfaces (p=.035) and on dynamic surfaces (p=.007), both after intervention, but no intergroup significant difference was found regarding bipedal stance.

QUALITY OF LIFE

Four studies used the European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30 (EORTC QLQ-C30). First, Bland and colleagues (135) showed an intergroup significant difference in favor of the immediate exercise group after intervention (p=. 05). Second, Streckmann and colleagues (138) reported

an intergroup significant difference in favor of IG during middle chemotherapy (p= .03), although there was no significance difference after intervention. Two studies did not report intergroup significant differences in quality of life at any time point (134,139). Other study measured quality of life using the Trial Outcome Index (TOI) of the FACT/GOG-NTX and reported intergroup significant differences in favor of IG after intervention (p= .028) and at follow-up (p= .031) (68).

RISK OF BIAS AND QUALITY OF DATABASES

The results of the assessment of risk of bias of the eight included RCTs are shown in Figure 2. Overall, most of the included studies had a high risk of bias in the overall bias assessment. The main methodological quality issue was outcome measurement, with "high risk" for a total of six of the eight studies (75%). Similarly, all of the included studies presented some concerns or a “high risk” of bias in the selection of the reported results. Therefore, none of the studies achieved a “low” overall risk of bias; one study demonstrated the least bias(68) (Figure 3).

Figure 2. Risk of bias graph: review authors' judgments about each Risk of Bias item presented as percentages across all included studies.

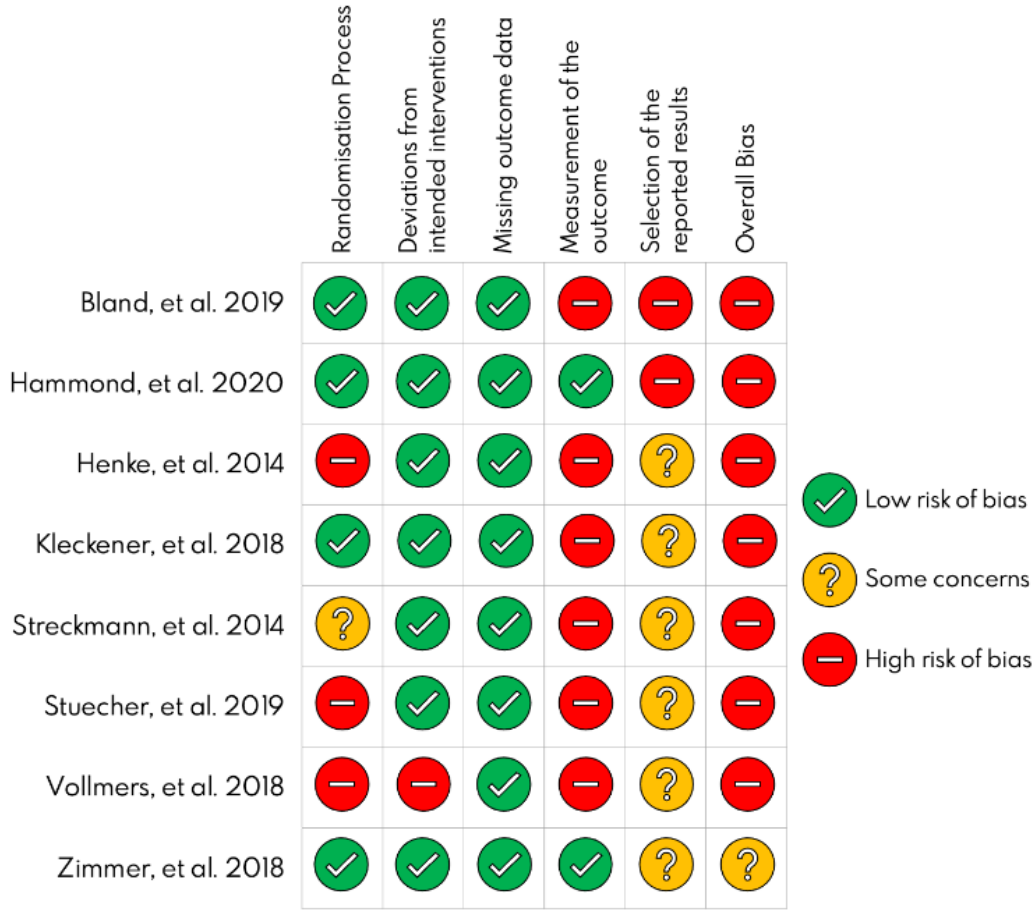
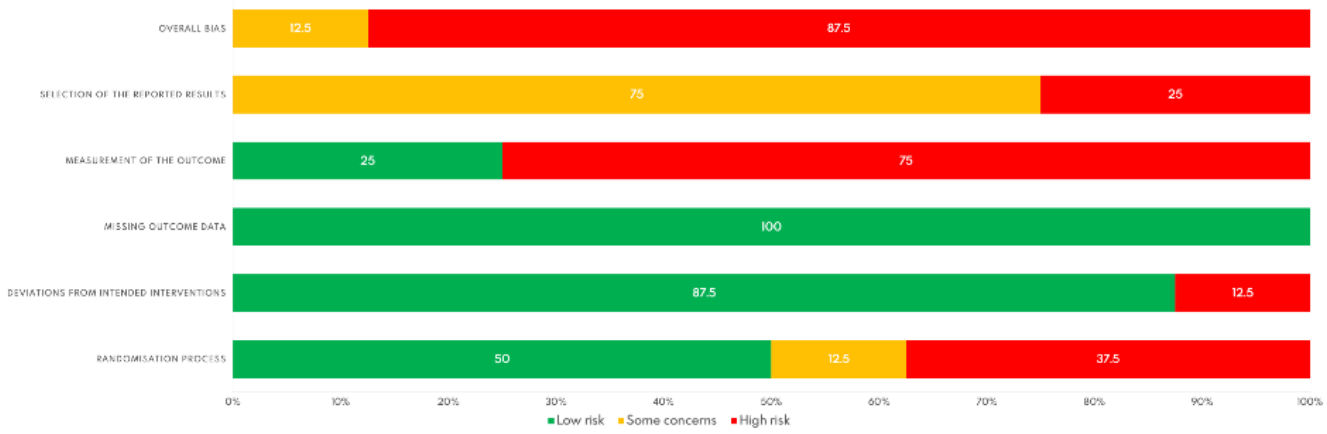


Figure 3. Risk of bias of RCTs included.



SENSITIVITY AND PRECISION OF EACH DATABASE

The database that reported the majority of results was Scopus, although it had the lowest precision (Table 4). It was also the database that found the highest sensitivity together with Medline. None of the databases identified unique hits.

Table 4. Sensitivity/precision analysis for each database

Databases	Total hits retrieved	Relevant hits retrieved	NNR	Unique hits	Sensitivity	Precision
Medline	68	3	23	-	33.33	4.41
Scopus	119	3	40	-	33.33	2.52
WOS	34	2	17	-	22.22	5.88
Cochrane	8	0	-	-	0	0
TOTAL	**229**	**8***				

Number asterisked (*) include total number of hits after duplicates removed.

NNR: Number Needed to Read (total hits retrieved/ relevant hits on a database).

Unique paper: relevant study retrieved from one database only.

Sensitivity: relevant hits retrieved / relevant hits retrieved TOTAL (%).

Precision: relevant hits retrieved / total retrieved (%).

META-ANALYSIS

Of the six studies in the systematic review that measured quality of life, it was only possible to include four in the meta-analysis (68,135,138,139). Three studies reported scores on the EORCT QLQ-C30(135,138,139) and the TOI(68). Their scores all ranged from 0-100 before and after the physical exercise program, adding a total of 137 participants (66 in the intervention group and 71 in the control group). To homogenize the sample and include only control group studies, the "end of chemotherapy" evaluation was used in the study of Bland and colleagues (135) since one of the two groups can be considered a control up to that point. The overall pooled results showed a statistically significant improvement in quality of life after the intervention (mean difference: 14.62, 95% CI 6.03, 23.20; I2: 0.00%, p-heterogeneity = .60) Pooled results are presented in Figure 4. To investigate whether the treatment estimate is robust when any of the studies are excluded and to explore the possible source of the heterogeneity, a sensitivity analysis was performed that excluded one study at a time. This analysis showed no substantial alteration of the main results. Given the number of articles included (below 10), publication bias was not possible (141). Additionally, Hegdes' g effect size was calculated in a secondary meta-analysis in which Bland and colleagues (135) and Streckmann and colleagues (138)

obtained the largest effect size (g= 1.57, 95% CI .71, 2.44 and g=.80, 95% CI .26, 1.34, respectively) (Figure 5).

Figure 4. Forest plot of studies analyzing effects of physical exercise vs usual care on the quality of life (x-axis: standardized mean difference; yaxis: studies included)

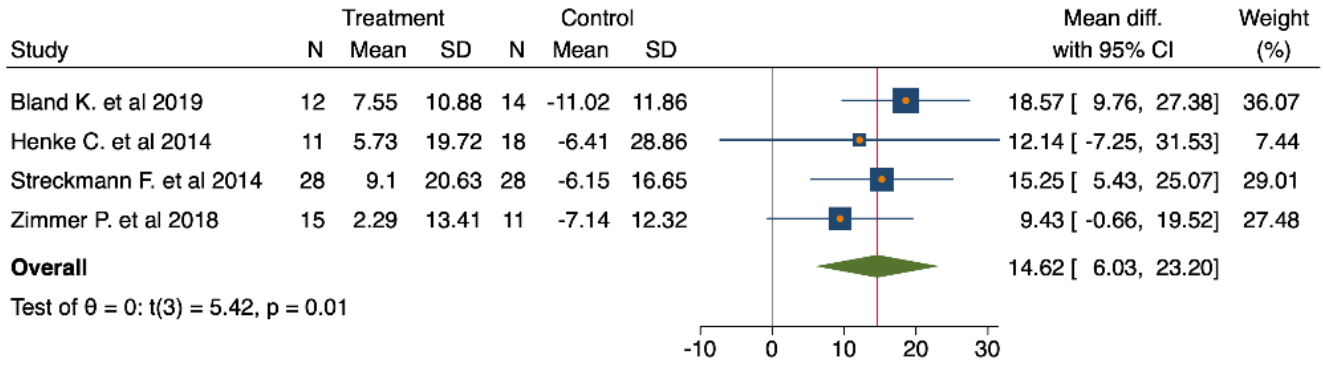
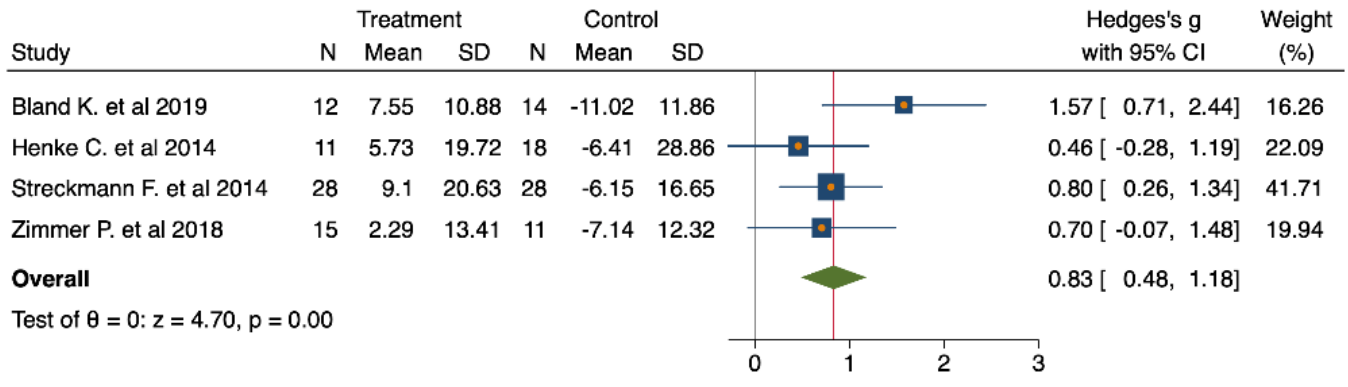


Figure 5. Forest plot of studies analyzing effects of physical exercise vs usual care on the quality of life (x-axis: effect size (Hegdes' g); y-axis: studies included).



Section II

Propose a physical exercise program with the capacity to prevent neuropathy (PRESIONA)

Study II

Prevention of Chemotherapy-Induced Peripheral Neuropathy With PRESIONA, a Therapeutic Exercise and Blood Flow Restriction Program: A Randomized Controlled Study Protocol

AIMS

Therefore, given the current evidence, our hypothesis is that implementing a tailored program called **PRESIONA** that combines physical exercise and BFR to prevent CIPN, which involves preconditioning of the musculoskeletal and nervous system, will alleviate the stress of chemotherapy.

The overall objective is to analyze the acute and cumulative effects of **PRESIONA** in patients with Breast Cancer undergoing neoadjuvant chemotherapy and determine the impact on the onset and severity of CIPN, quality of life, sensorimotor and physical functional outcomes, and proportion of completed scheduled chemotherapy sessions.

METHODS

STUDY DESIGN

This is a study protocol of a randomized controlled trial that has been developed following the recommendations of the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT)(142), the Consolidated Standards of Reporting Trials (CONSORT) Statement(143) and the Template for Intervention Description and Replication (TIDieR) checklist(144). The

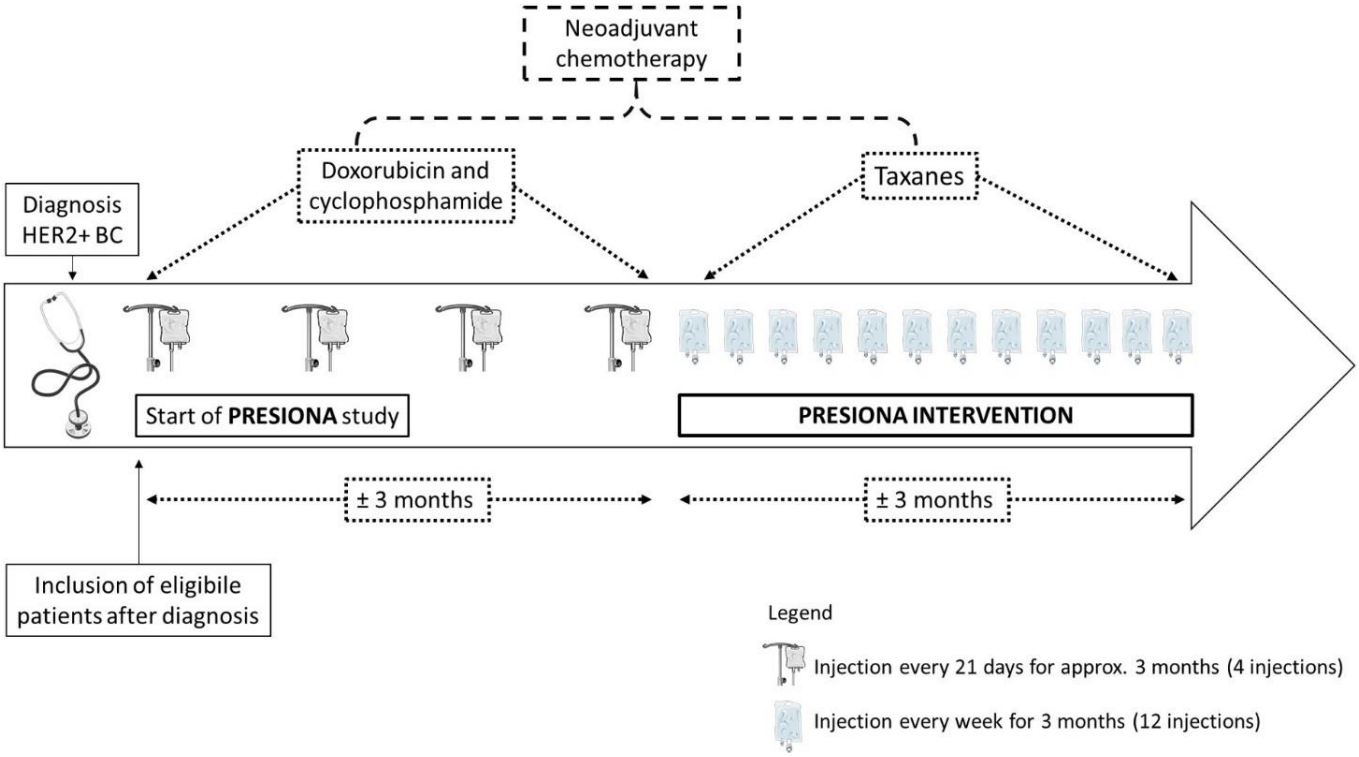
PRESIONA trial was registered with ClinicalTrials.gov (code: NCT04652609)(145).

An efficacy study will be performed based on a randomized controlled trial design of two parallel groups, including an experimental group and a control group, to examine both the acute and cumulative effects of the **PRESIONA** program. The entire protocol of the present study will be performed at the 'Cuidate Support Unit for Oncology Patients (CUIDATE)', a research center specializing in oncology rehabilitation that is part of the 'Sport and Health University Research Institute' (iMUDS) of the University of Granada, Spain.

Prior to the efficacy study, a feasibility study will be conducted due to the novelty of the study using a prospective, longitudinal, quasi-experimental, prepost, one-arm design to investigate the recruitment, retention, satisfaction, acceptability, and safety of the program.

The study population will be patients diagnosed with early breast cancer identified by oncologists (Figure 1). Patients will be recruited from the oncology unit of San Cecilio University Hospital in Granada, Spain.

Figure 1. Representation of treatment schedule and study inclusion for patients with HER2 positive breast cancer.



ELIGIBILITY CRITERIA

The inclusion criteria will be (1) patients with confirmed HER2+ subtype breast cancer, (2) patients over 18 years of age, and (3) patients waiting to receive neoadjuvant chemotherapy. The exclusion criteria will be (1) previous diagnosis of cancer, (2) pregnancy, (3) cardiac pathology, (4) symptoms or pathology that could be confused with neuropathy or related to diabetes and (5) a recommendation from an oncologist against physical exercise practice.

INTERVENTION

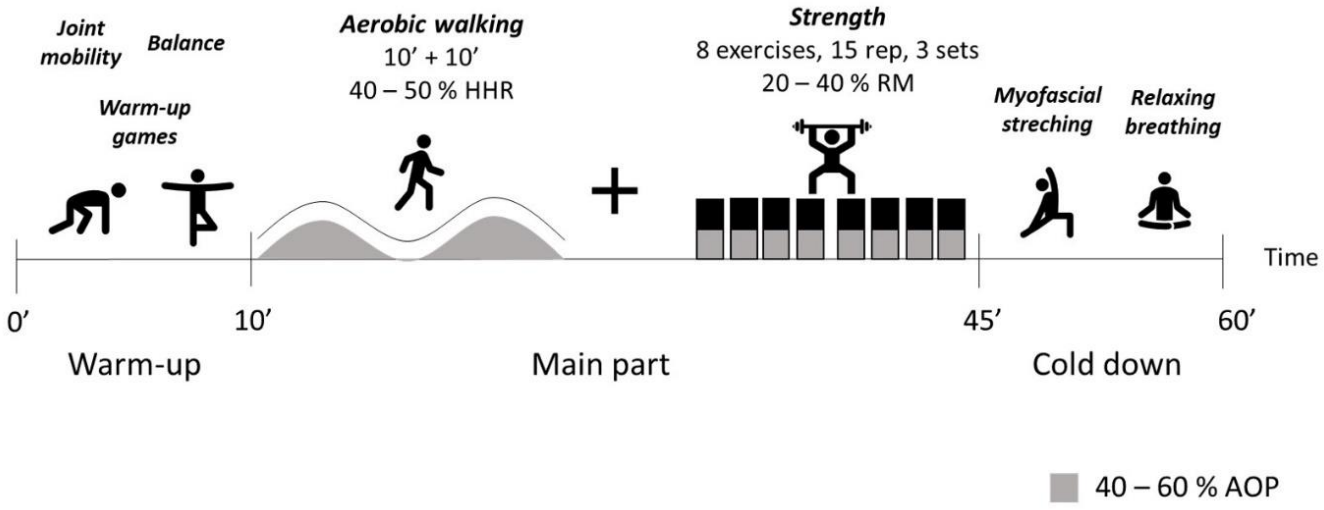
PRESIONA will be a physical therapy-led multimodal exercise program that applies BFR during concurrent exercise (aerobic and strength exercises). The program consists of 24-36 sessions over 12 weeks following an undulatory prescription based on the physical stimulus assimilation of each patient using the ATOPE+ mobile application(146). Each patient must attend at least 2 weekly sessions up to a maximum of 3 on alternate days. **PRESIONA** has been designed by physical therapists with experience in BFR prescription who specialize in physical exercise in patients with cancer.

The sessions will be face-to-face and last approximately 1 hour with three parts: warm-up, main part and cooling-down period (Figure 2). Balance proposals and mobility will be included in the warm-up. The balance proposals will progressively increase the complexity of the task from low to high (monopedal position, eyes closed, instability on the surface) for three sets of 20 seconds, allowing for rest between sets (intra- and intersets)(147). To avoid injuries, patients will be secured by the physical therapist. The main part involves low-medium intensity physical exercise, including aerobic work at 40-50% heart rate reverse (HRR) using an elliptical machine and eight resistance full-body exercises with a focus on the intrinsic muscle of the

hands and feet at 20-40% RM. During this part, patients will wear occlusion cuffs (KAATSU cycle 2.0, KAATSU Global, Inc, California) that will reduce the arterial blood flow up to 60% of arterial occlusion pressure (AOP) of the muscles that are working at that moment. Perfusion will be normal during rest.

Progression will be determined according to ATOPE+, which is a mobile application developed(148) and registered by our research group (https://ieeexplore.ieee.org/document/9314150). ATOPE+ recommends physical exercise depending on the recovery assessed with different objective and subjective tools. After registering in the morning, the researcher receives information on the state of recovery. The aim is to ensure that whenever a subject participates in **PRESIONA** is in a state of recovery.

Figure 2. Schematic representation of one session of PRESIONA program. Each session will have three parts (warm-up, main part and cold down). The main part is composed of 20 minutes of aerobic walk and a strength phase where load will be applied to the upper and lower limbs. The grey colour represents when the occlusion cuffs will be applied. % AOP: calculated percentage of arterial flow; HRR: heart rate reserve; RM: repetition maximum.



To determine the BFR pressure (mmHg), a vascular Doppler ultrasound probe (Samsung HM70A) will be placed acrally over the tibial artery or radial artery of the lower or upper limbs while subjects are in a relaxed standing position (149). A KAATSU cuff attached to the proximal portion of the limb will be automatedly inflated to the point at which the auscultatory pulse of the artery is interrupted (10-mmHg precision) (150–152).

For ethical reasons, participants in the control group will be told they can participate in other research studies, but their information will be recorded

for inclusion in the analysis. Importantly, any physical activity performed in the control group will be recorded.

OUTCOME MEASUREMENTS

FEASIBILITY STUDY

The recruitment-acceptance ratio will include the number of potentially eligible and recruited patients. Reasons for nonparticipation will be recorded. Additionally, the rate of dropouts, the reasons for not attending the program and the preferences or needs that would drive patients to participate will also be recorded. The retention rate will be calculated based on patients who complete at least 75% of the program(153).

Adherence will be assessed using an attendance diary collected by the physical therapist. The threshold will be 75%(154).

Participant satisfaction will be registered using a MEDRISK questionnaire (155) consisting of 20 items and with a Cronbach's α of on .90, which will be conducted after discharge from outpatient physical therapy care.

Program tolerance will be quantified by measuring the pain produced by the occlusion using the visual analog scale (VAS, 0-10). BFR may be painful (97);

the pressure used will be lower (40-60% of limb occlusion pressure) to minimize possible pain. Otherwise, if a patient cannot tolerate occlusion will be withdrawn from the study. The analysis will be performed on an intention-to-treat principle.

Program safety will be assessed by recording the incidence and severity of adverse events using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. (156). Every week, patients will answer an online questionnaire to report any adverse events that they interpret as concerning. The answer will be monitored and saved by a medical oncologist, and this person will consider whether the adverse events are related to the intervention. Adverse events, such as cardiovascular responses (e.g., hypertension, ischemia), exertional symptoms and musculoskeletal symptoms (157), could be expected, bearing in mind that we expect some adverse events given the fact that patients are undergoing chemotherapy (158).

EFFICACY STUDY

MAIN OUTCOME

The Spanish version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20-item scale (EORTC QLQ-CIPN20) will be used to

assess patient-reported CIPN across sensory, motor, and autonomic domains. The total questionnaire score ranges from 0 to 100, and a higher score indicates increased symptom burden (159). The sensory and motor subscales have good reliability, obtaining Cronbach's α values of .87 and .83, respectively (160).

SECONDARY OUTCOMES

PATIENT-REPORTED HEALTH OUTCOMES

The European Organization for Research and Treatment of Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23) will be provided to measure cancer-specific indices of quality of life based on 23 items. The scoring is the same as that noted for the previous questionnaire, and the assessment has a Cronbach's α between .46 and .94 (161).

The clinical version of the Total Neuropathy Score (TNSc) will be used to monitor and assess CIPN severity and progression (162). The assessment includes muscle weakness and numbness and tingling in the hands and feet as well as pinprick sensibility, vibration sensibility, tendon reflexes, and strength assessments. The total score ranges from 0 to 24 points; a higher

score indicates greater neuropathy severity. Its intraclass correlation coefficient (ICC) ranges from .85 to .87 (163).

To evaluate the quality of sleep, we will use the Spanish version of the Pittsburgh Sleep Quality Index (PSQI) (164), which consists of 19 self-reported items and 5 questions reported by a roommate of the patient. Items are grouped into seven subjective dimensions, and the total score ranges from 0 to 21. Higher scores indicate worse sleep quality. In the population with breast cancer, the Cronbach α is .80 (165).

Pain in the hands and feet will be measured using the VAS. Participants will be asked to mark the level of pain felt at that moment on a linear scale with a length of 10 cm. The VAS has been widely used in cancer patients (166).

SENSORIMOTOR OUTCOMES

Touch detection thresholds will be measured using Semmes-Weinstein filaments (SWMs) (North Coast Medical Inc., Morgan Hill, CA, USA). The fibers (1.65 to 6.65 gauge) will be applied perpendicularly to a skin area following a previously published protocol (167). For each point, the smallest monofilament perceived by patients shall be recorded and will be analyzed as

frequency and percentages of patients. SWMs are a valid tool to identify subclinical peripheral neuropathy in oncology patients (167).

The Purdue Pegboard Test (Lafayette Instrument Co., Lafayette, USA) will be used to evaluate fine manual dexterity and sensorimotor function (168). The number of pins a patient can place in the holes using both hands in 30 seconds will be recorded as a function of manual dexterity according to the instructions in the user's manual. This test is recommended to evaluate patients who suffer from CIPN (169).

PHYSICAL FUNCTION OUTCOMES

The 6-min walk test (6MWT) is a widely validated measure of general physical functioning and mobility. Patients are instructed to walk between two markers set 30 m apart as many times as possible over 6 minutes. A greater distance covered indicates greater mobility and general functioning (170). The 6MWT has been validated in patients with cancer with an ICC of .93 (171).

We will use the handgrip strength test using a TKK5101 Grip-D dynamometer (Takeya, Tokyo, Japan) to assess the muscle strength of patients following a previously established protocol (172). Patients will be asked to grip the

device and squeeze it three times as hard as possible, and they will be allowed to take breaks between attempts. Three mean values will be determined in kilograms for both hands. This test has been previously used in patients with breast cancer (173).

The Mini-Balance Evaluation Systems Test (Mini-BESTest) includes 14 items involving dynamic balance tasks. A maximum of 28 points is possible with higher scores signifying better balance (174). This test has been validated in patients with cancer with an ICC of .86 (175).

BODY COMPOSITION AND ANTHROPOMETRIC OUTCOMES

Muscle mass (kg), body fat (%) and body weight (kg) will be assessed using the InBody720 bioelectrical impedance device (Biospace, Seoul, Korea) following the indications of the user's manual (176). This technique has an ICC of .95 for muscle mass and .93 for body fat in women (177).

CHEMOTHERAPY COMPLETION

We will also report the ratio of the number of chemotherapy program sessions and the number of completed sessions.

SAMPLE SIZE

For both the acute and cumulative studies, sample sizes were calculated based on patient-reported CIPN using the minimal clinically important difference of the sensory and motor subscales, respectively (178). In both analyses, a confidence level of 95%, a statistical power of 85% and one-sided alpha of 5% were considered. The literature on physical exercise and cancer supports the decision to perform a one-sided test for sample size calculation; it is a novel intervention, but physical exercise is also widely employed in the breast cancer population and it is known that participation in this program will be positive. An effect size of .66 (d) has been reported to detect differences in the first cycle of taxane-based chemotherapy in patients with breast cancer; hence, 34 participants will be needed per group. Considering a dropout rate of 5%, 72 patients will be included in the acute study. For the cumulative study, a .70 effect size (d) is expected in patients one year from the start of chemotherapy (178); therefore, 31 participants will be needed per group. Due to a potential dropout rate of 30% (153), at least 40 patients will be required for each group with 80 in total.

RANDOMIZATION AND BLINDING

Following successful completion of baseline assessments, patients will be randomized and allocated by a blinded researcher using two concealed lists generated with random numbers with a 1:1 distribution. Assessments will be performed by a blinded assessor. However, the research staff responsible for delivering the intervention and allocating participants will not be blinded.

DATA COLLECTION AND MANAGEMENT

Patients will be evaluated at baseline 24 hours prior to the first chemotherapy session (t0) and in the next 24 hours after the first chemotherapy session (t1) in the acute study.

With regard to cumulative effects, patients will be assessed at five time periods: at baseline (after diagnosis) (t0), after anthracycline completion (t1), at the end of chemotherapy (t2), and at the 2-month (t3) and one-year (t4) follow-ups (Figure 4).

Figure 4. Details of enrolment, intervention and assessments according to the SPIRIT diagram.

	STUDY PERIOD						
	Post breast cancer diagnosis			***During neoadjuvant chemotherapy***		***End of chemotherapy (follow-up)***	
	Enrollment	***Baseline***	***Allocation***	***Pre intervention***	***Post intervention***	***2-month follow-up***	***1-year follow-up***
TIMEPOINT	***-t1***	***t0***	***0***	***t1***	***t2***	***t3***	***t4***
ENROLLMENT							
Eligibility screening	X						
Informed consent	X						
Allocation			X				
INTERVENTIONS							
PRESIONA				←	→		
Control group				←	→		
ASSESSMENTS							
Feasibility							
Recruitment-acceptance ratio	X						
Rate dropouts						X	

Retention						X	
Adherence						X	
Satisfaction						X	
Tolerance						X	
Safety						X	
Efficacy							
CIPN symptoms		X		X	X	X	X
Quality of life		X		X	X	X	X
Severity of CIPN		X		X	X	X	X
Quality of sleep		X		X	X	X	X
Mood		X		X	X	X	X
Pain		X		X	X	X	X
Quantitative sensory testing		X		X	X	X	X
Manual dexterity		X		X	X	X	X
Handgrip strength		X		X	X	X	X
Physical functioning		X		X	X	X	X
Balance		X		X	X	X	X
Body composition		X		X	X	X	X

ETHICS

The study was approved by the Ethics Committee of the Junta de Andalucía (1674-N-20) according to the Helsinki Declaration for biomedical research. All participants will provide informed consent.

STATISTICAL ANALYSES

Preliminary descriptive analyses will be used for visualization of sociodemographic and clinical data from the two groups, and the results will be presented as means and standard deviations for continuous data and frequencies and percentages for categorical data. The normal distribution will be assessed using the Kolmogorov or Shapiro Wilk test. For baseline comparisons, Student's t / Mann-Whitney U tests will be used for continuous variables; and $\chi 2$ / Fisher's exact tests will be used for categorical variables, as appropriate. Regarding feasibility, the proportions, percentages, and Student's t or Mann-Whitney U tests results will be reported, as appropriated. For the efficacy study, acute effects will be assessed by analyzing two assessments (t0 - t1) using a univariate general linear model. For cumulative effects, repeated measures analysis of covariance (ANCOVA) followed by post hoc analysis with Bonferroni adjustment will be used. For both effects,

body composition, anthropometric characteristics and age will be considered covariables. Whether anthracyclines produce any effect on CIPN will be analyzed (t0 - t1). Then, the main effect of the intervention will be measured as (t1 - t2). If the main effect is maintained over time, it will be observed as (t1 - t3 and t1 - t4). Potential missing outcomes will be analyzed according to the intention-to-treat principle(179), where multiple imputations will be performed(180). Calculations of the intergroup effect sizes will be performed to provide magnitude changes; the effect size will be estimated using Cohen d (0-.19, negligible; .20–.49, small; .50–.79, moderate; ≥.8, large) (181). All analyses will be performed using IBM© SPSS© Statistics. Significance will be set at $p<.05$.

DISCUSION

In 2022, a bibliometric analysis revealed the potential of some non-pharmacological therapies, such as physical exercise, to address CIPN, pointing to the development of these possible lines of research as a key point in the advancement of knowledge in the area (182). In line with this, in the **Study I** presented in this thesis report, we analyze the effects and types of physical exercise programs in cancer patients undergoing chemotherapy and their relationship with CIPN prevention.

The results of this study reinforced the previous idea, showing that physical exercise has shown promising effects on the prevention or amelioration of CIPN when it was prescribed from the start of chemotherapy treatment chemotherapy. The results of the meta-analysis present also positive effects of physical exercise programs on improving cancer-related quality of life compared to usual care. After this review, the result of this analysis is in line with the recommendations of other studies indicating that exercising regularly (aerobic and resistance exercise) at the onset of neurotoxic treatment (183) and providing balance training (184) to avoid CIPN.

Specifically, the results of these studies to improve quality of life in patients with cancer who start potentially neurotoxic chemotherapy can be summarized following the FITT method: (F) at least two sessions per week (68,135,138), (I) with a range of 60-80% HR max (68,185) or 50-75% HRR (135,139) for aerobic exercise, while the resistance rate should be between 50-80% 1RM estimated (68,135,185), (T) multimodal (endurance, resistance and balance) physical exercise should be supervised, (T) each session should last maximum one hour (68,135,185) and ranged from eight to twelve weeks (68,135,185). For patients with inoperable lung cancer, the physical exercise program could coincide at least during chemotherapy cycles, increase the number of sessions per week (up to six) and reduce the time during the session (up to 8 minutes) (139). For these recommendations the largest estimated

effect size in quality of life was found by Bland and colleagues in patients with breast cancer (*g*= 1.57) (135); in which the completion of the physical exercise program finished before chemotherapy, that is, prehabilitation. In addition, the second one was performed by Streckmann and colleagues (138) in patients with lymphoma (*g*= .80).

Analyzing the recommended FITT prescription, we found that the frequency was in accordance with the international guidelines for physical activity and cancer (186). In this review, six studies that reported results in favor of physical exercise programs met the moderate intensity of aerobic exercise (68,134,135,137,138,140). Although this makes it difficult to identify a definitive intensity recommendation, it is important to note that regardless of the intensity used, there were no adverse effects reported in any of the reviewed studies. With regard to resistance exercise, adding this proposal is related to a reduced risk of all-cause mortality in patients with cancer (187). There was more coincidence around the intensity, the volume and the exercises used, which were highly analytically oriented to the lower or upper limbs (68,137). Despite all of its benefits, we detected a decrease in adherence when resistance proposal was added, although in general adherence was high; according to the authors' criteria (> 75%) (188), in our review, the average adherence was 80%. Finally, our results suggest that multimodal physical exercise programs have more

benefit; along this line, aerobic proposal has been recommended as a key component of physical exercise programs to treat CIPN by other authors (71). Supervision of the modality by a healthcare professional could be more appropriate if balance task is included to avoid falls (189) because none of the home-based programs included balance proposals.

For pain relief, concurrent home-based programs could be recommended accompanied by nerve gliding exercise. Nerve gliding exercises can reduce neural edema, decrease pressure and restore function by improving pain (190). The acute effect of nerve gliding exercise, associated with the effects of physical exercise (56), is hypoalgesia; therefore, it may be a complement in programs whose objective will be to prevent CIPN, but there is also neuropathic pain. However, a small effect size was obtained in this review in physical exercise intervention (d=0.46) (137). Looking at measurements, the VAS is a widely used tool to assess pain (191) and it is strongly recommended for either pain or heat/cold symptoms in patients undergoing chemotherapy.

Curiously, although vibration impairments are a characteristic symptom in patients suffering from CIPN (36), in the reviewed studies, this was a difficult symptom to evaluate. None of the three articles used the same measurement method, and only

two studies found significant improvements, but not at the same measured time point. In view of these results, we encourage consensus in following the ACTTION recommendations (118) that emphasize the measurement of vibration within the Total Neuropathy Score scale.

In relation to the assessment of CIPN, we can only cautiously recommend that CIPN assessment be measured with TOIs (68). The neurotoxicity score of TOI is not structured to differentiate between changes in positive or negative neuropathic symptoms and instead proves its worth evaluating treatment-related neurotoxicity (192). This could explain the good intergroup results, and TOI could be a useful tool for follow-up measurements.

Similarly, regarding balance, few studies measured it, or they reported global analysis of the balance test, which can make it difficult to find more explicit differences in more challenging balance tasks (68). However, one study showed significant benefits in global balance after a physical exercise program compared to usual care (134). All studies that measured sway area, especially monopodal sway (either on static or dynamic surfaces), found improvements in the group who performed physical exercise compared to the control group. Highlighted the Stuecher and colleagues study that showed an estimated medium and large effect size using a walking

proposals in the middle of chemotherapy (d= .59) and after intervention (d=.95) (140). It is known that CIPN patients use less proprioceptive information, entailing less accurate sway area (38). In our review, physical exercise, especially when the balance proposal is included, can partially correct sway area damage by chemotherapy. This finding is in line with other studies (193,194).

We were unable to analyze every outcome in the meta-analysis due to the heterogeneity of both outcomes and programs; therefore, only quality of life was selected. Three of the four studies included in the meta-analysis were very similar in terms of FITT method prescription (68,135,138); therefore, the heterogeneity of the meta-analysis was absent (.00%). In this sense, the results of the meta-analysis support, from a quantitative point of view, the evidence for the benefits of physical exercise in improving quality of life when performed at the start of chemotherapy. All included studies support this conclusion, in line with other authors (58,195,196). In contrast, these results should be viewed with caution because none of the four included studies were free of bias. The biggest problem was in reference to measurement of the outcome and selection of the reported results due to the lack of previously published or registered study protocols. Sensitivity analysis of metanalysis performed by excluding one study at a time showed that the exclusion of studies with more or less risk of bias did not affect the results (197).

To the best of our knowledge, sensitivity/precision analyses to identify relevant databases have never been documented within this area. Despite efforts, the sensitivity and precision of most of the databases were very low; we believe that the lack of the concept of 'CIPN' in the thesauri of notable databases such as Medline and Cochrane influenced our results. We recommend studying its inclusion given the relevance of the topic.

Regarding **Study II**, we planned this study because many methods tested for the treatment of CIPN have not yet achieved the expected results (40). The prevention of CIPN would have an impact on quality of life and reduce healthcare costs associated with CIPN in patients with breast cancer as a consequence of loss of labor force, outpatient visits and time spent in the hospital (39). The most promising nonpharmacological intervention to prevent CIPN is physical exercise (70,117). However, there are many gaps in identifying the exercise parameters that provide the greatest benefit for the prevention of CIPN (122). Furthermore, it must be ensured that these studies are safe and can be easily performed.

In fragile populations, physical exercise with BFR is a useful and safe method to improve various aspects related to the physical health of the patient, such as cardiorespiratory function, hypertrophy, and weight loss(80,98). Given the results

demonstrated in other populations, introducing BFR into multimodal exercise programmes -**PRESIONA**- could emphasise/reinforce their effects as a method of targeted preconditioning in areas primarily affected by neurotoxicity,

Additionally, this study is one of the first to explore a battery of common clinical measures recommended in prevention trials for CIPN (118). It is expected that this study will provide an improved understanding of the role that physical exercise and BFR training can play in providing an efficacious, time-efficient modality of exercise for patients with breast cancer. In addition, our patients will be monitored using the ATOPE+ app (198) to ensure healthy doses of exercise. The clinical reason to implement **PRESIONA** is to achieve greater therapeutic success and improve the quality of life during and after medical treatments given the active involvement of the patients in their own health. **PRESIONA** could be easily integrated into public healthcare; in fact, physical activities reduce Public Healthcare costs (55). The physiotherapist is a key professional in multiprofessional care teams in the management of people with cancer (199), with an essential intervention not only in the evaluation, but also in the prevention and treatment in patients suffering from CIPN (200).

An unstated objective of **PRESIONA** is to achieve the promotion of physical activity and autonomy or self-care in the practice of physical exercise in breast cancer patients. Thus, in those patients in whom prevention is not achieved, CIPN can persists several years after cessation of chemotherapy but it is significantly reduced by exercise in a dose-dependent manner (201).

STRENGTHS AND LIMITATIONS

The strengths of the **Study I** were as follows: a meta-analysis was made; the reporting was made according to the PRISMA guidelines; risk of bias assessment was included; previously registered in PROSPERO and sensitivity/precision analyses data bases was conducted. One of the first analyses in a very broad way very concrete aspects following FITT prescriptions recommended by the roundtable (202), this is in line with the expected quality standards in exercise interventions in oncology patients. The limitations include the following: none of the studies achieved low overall risk of bias assessments and heterogeneity in outcomes; the majority of the patients were women with breast cancer receiving taxane-based chemotherapy, which limits the generalizability of the data. Besides, one of the main objectives, to identify the specific parameters of physical exercise programs that provide prevention of CIPN in patients with cancer was not answered completely because heterogenicity of outcomes.

With regards **Study II**, the reporting will adhere to the CONSORT and SPIRIT guidelines, and the proposed outcomes are gold standard for CIPN assessment. In order to promote transparent evidence, the protocol was registered in Clinicaltrials.gov. In addition, it has a strong neurophysiological basis, high potential by combining methods with a lot of evidence and it is focus on prevention. In contrast, the **PRESIONA** study consists of a primary prevention design, which provides the highest likelihood of success if the therapy cannot reverse or delay the progression of the established damage, but participants will be exposed to unnecessary therapy (118). Additionally, it is possible that the impact of diagnosis could cause denial before the trial's enrollment.

FUTURE STUDIES

Future studies should report what total dose of chemotherapy was received during the intervention due to dose-dependent toxicity (9). Additionally, we believe that the main problem of these studies has been delimiting the onset of CIPN with a unique outcome. A single dose may damage the peripheral nervous system (203), but patient-reported onset does not occur until 60 days after chemotherapy (204). An assessment not made after 60 days could be responsible for missing true cases of CIPN. For this reason, follow-up measurements are planned for **Study II**.

For efficacy studies, comparison of outcomes should be based on cut-off points and clinical relevance as set out in expert guidelines, in particular physiotherapists can follow the proposed framework published in 2023 (200). Also, future studies could take into account which databases to consult, Medline and Scopus are the most sensitive, although WOS is the most accurate for our topic. Interventions focused on patients at high risk of CIPN should begin before the initiation of neurotoxic treatment.

CONCLUSION

In summary, the review in **Study I** presents all physical exercise programs to date to prevent CIPN and establishes the essential dose for clinicians and patients for success. Supervised multimodal physical exercise is feasible and has the potential to improve quality of life and prevent CIPN symptoms in patients with cancer undergoing chemotherapy. The role of the rehabilitation staff is to address side effects mostly after the completion of treatments, and they could propose prehabilitation interventions to control the impact of treatments against cancer.

The proposed innovative approach of **the Study II** will have a far-reaching impact on therapeutic options. Physical therapists in the health system could be essential to

achieve the planned doses of chemotherapy to improve survival and decrease the side effects of breast cancer (205). This protocol could provide an action guide that could be implemented in various healthcare settings.

CONCLUSIÓN

En resumen, la revisión sistemática con meta-análisis del **Estudio I** sintetiza todos los programas de ejercicio físico realizados hasta la fecha para prevenir la neuropatía inducida por quimioterapia y establece la dosis esencial para que tantos clínicos y pacientes tengan éxito. El ejercicio físico multimodal supervisado es factible y tiene el potencial de mejorar la calidad de vida y prevenir los síntomas derivados de la neuropatía periférica en pacientes con cáncer tratados con quimioterapia. Hasta ahora, el rol del personal de rehabilitación ha sido abordar los efectos secundarios sobre todo tras la finalización de los tratamientos, y podría haber un cambio de corriente para proponer intervenciones de prehabilitación para controlar el impacto de los tratamientos contra el cáncer.

El enfoque innovador (restricción del flujo sanguíneo más ejercicio físico de baja intensidad/carga) propuesto en el **Estudio II** podría tener repercusiones

de gran alcance en las opciones terapéuticas. Los fisioterapeutas en el sistema sanitario podrían ser esenciales para alcanzar las dosis planificadas de quimioterapia para mejorar la supervivencia y disminuir los efectos secundarios del cáncer de mama (205). Este protocolo podría proporcionar una guía de actuación que podría aplicarse en diversos entornos sanitarios.

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