REVIEW ARTICLE

HIGH-INTENSITY TRAINING AND CARDIOVASCULAR TOXICITY IN CANCER

ENTRENAMIENTO DE ALTA INTENSIDAD Y TOXICIDAD CARDIOVASCULAR EN CÁNCER

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RESUMEN

Introducción: La sobrevida en los pacientes oncológicos cada vez tiene mayor porcentaje, así como la prevalencia de enfermedades cardiovasculares a consecuencia del tratamiento antineoplásico; el diagnóstico oportuno y la intervención de manera interdisciplinaria, siendo fundamental para disminuir y/o prevenir afectaciones cardiovasculares. **Objetivo:** Determinar el impacto del entrenamiento de alta intensidad en la toxicidad cardiovascular en cáncer. **Materiales y métodos:** Se realizó una revisión sistemática descriptiva cronológica y retrospectiva de artículos analizados entre 2018 a

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2022, de acuerdo con los criterios de la declaración de PRISMA y valorando la metodología bajo los criterios de la escala PEDro. Se recaudó información de la población, características de los grupos, intervención, efectos y resultados. **Resultados:** Se analizaron 9 ensayos clínicos, con un total de 724 participantes oncológicos bajo el tratamiento quimioterapéutico, y se encontró que el entrenamiento HIIT mejoró la fracción de eyección (39.6±7.3 vs 46.5±2.4; *p*= 0.005), frecuencia cardíaca máxima (154.0±13.0 vs 168.5±8.0; *p*= 0.005), presión arterial sistólica (133.5±6.2 vs 122.0±1.6; *p*= 0.005), presión arterial diastólica (86.5±10.3 vs 81.0±2.4; *p*= 0.005). Además, aumenta los niveles de vo2, fuerza y disminuye la fatiga asociada al cáncer, entre otras variables más. **Conclusión:** El HIIT no solo conduce a mejoras significativas en la capacidad funcional y la calidad de vida, sino que también emerge como una estrategia potencialmente prometedora para prevenir la cardiotoxicidad asociada con las terapias antineoplásicas.

Palabras clave: *Cardiotoxicidad, ejercicio de alta intensidad, fisioterapia.*

ABSTRACT

Introduction: Survival in oncology patients has an increasing percentage, as well as the prevalence of cardiovascular diseases because of antineoplastic treatment; timely diagnosis and intervention in an interdisciplinary manner, being essential to reduce and/or prevent cardiovascular conditions. **Objective:** To determine the efficacy of high intensity training on cardiovascular toxicity in cancer. **Materials and methods:** A chronological and retrospective descriptive systematic review of articles analyzed between 2018 and 2022 was conducted, according to the criteria of the PRISMA declaration and evaluating the methodology under the criteria of the PEDro scale. Information was collected on the population, group characteristics, intervention, effects, and results. **Results:** Nine clinical trials were analyzed, with a total of 724 oncological participants under chemotherapy treatment, and it was found that HIIT training improved ejection fraction (39.6±7.3 vs 46.5±2.4; *p*= 0.005), maximum heart rate (154.0± 13.0 vs 168.5±8.0; *p*= 0.005), systolic

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blood pressure (133.5±6.2 vs 122.0±1.6; *p*= 0.005), diastolic blood pressure (86.5±10.3 vs 81.0± 2.4; *p*= 0.005). In addition, it increases VO2 levels, strength and reduces fatigue associated with cancer, among other variables. **Conclusion:** HIIT not only leads to significant improvements in functional capacity and quality of life, but also emerges as a potentially promising strategy to prevent cardiotoxicity associated with antineoplastic therapies.

Keywords: Cardiotoxicity, high intensity exercise, physiotherapy

INTRODUCTION

Cancer is a disease that affects millions of people worldwide (World Health Organization, 2022). It produces modifications and mutations in healthy cells to transform them to cancerous ones that proliferate uncontrollably and invade other tissues, affecting the physical, emotional and multisystemic integrity of the patient (Morales Y. et al. 2018). Although treatments have improved significantly in recent decades, cardiovascular toxicity remains a major concern.

The burden of cardiovascular toxicity in cancer patients is a multifactorial phenomenon, influenced by the disease itself and antineoplastic treatments. Current evidence indicates that chemotherapeutic agents, such as doxorubicin, can induce left ventricular dysfunction, increasing the risk of adverse cardiovascular events (Smith LA. et al. 2010). In addition, cardiotoxicity associated with targeted therapy, such as tyrosine kinase inhibitors, has been well documented, with effects on systolic and diastolic function of the heart (Force T. et al. 2011).

Because of the above, cardiovascular diseases (CVD), together with cancer are the main morbidity factors worldwide (Hameau R. et al. 2018). Evidence confirms that the mortality of cardiac toxicity due to oncological treatment is 3.5 times higher compared to idiopathic cardiomyopathies. Because of the above, cardiac functionality is one of the dose-limiting variables in treatment by contributing to morbidity and mortality (Chung R. et al. 2018).

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On the other hand, the effects of exercise in a general way in the oncology patient are the improvement of functionality, muscle strength and quality of life, reduction of the perception of fatigue induced by chemotherapy and decrease of pain, presence of nausea, vomiting, among others (Sara M. et al. 202; Mijwel S. et al. 2018). Another type of training performed in the rehabilitation area is high-intensity intervallic training (HIIT) (Mijwel S. et al. 2018). HIIT is one of the most effective training compared to traditional methodology, due to the changes it produces by improving functional and metabolic capacity at the musculoskeletal level and some cardiovascular risk factors (Lee K. et al. 2019) by reducing the stress on the cardiovascular system in healthy populations, which is the main contributor to anthracycline-induced vascular dysfunction (Koutsoukis A. et al. 2018; Abarzúa J. et al. 2019).

Therefore, high-intensity training has been proposed as a strategy to improve cardiovascular health in cancer patients. However, current evidence on the relationship between HIIT and cardiovascular toxicity in cancer patients is limited. Indeed, the research question of this systematic review is: What is the impact of HIIT training on cardiovascular toxicity in cancer, and therefore the main objective of the present investigation is: To determine the impact of HIIT on cardiovascular toxicity in cancer.

MATERIAL AND METHODS

Systematic review combined with a descriptive retrospective chronology analysis of randomized clinical trials taken between January 2018 to June 2022 in databases that were indexed, always taking care that, there was an informed consent under the ethical considerations of Helsinki used for medical research in humans.

A systematic review was performed in accordance with the criteria of the PRISMA statement *(Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) (Urrútia G. et al. 2010), using Boolean operators: AND & OR; stratifying the search as follows (*High-intensity training AND cardiovascular toxicity AND cancer*), (*High-intensity training AND*

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cardiovascular toxicity OR cancer), (*High-intensity training AND cardiovascular toxicity*), (*HITT AND cancer*), (*HITT AND cardiotoxicity*) as well as in Spanish in the PUBMED, Google Academic, EBSCO and PMC databases.

The search, extraction, analysis and examination was performed by one author (AD. J-G), reviewed by a second (D. P-F) and third (Z. T-C) author, as well as agreed upon by all the research collaborators. The selection of the studies was based on where oncological patients of different origin, sex, age, ethnicity or sociodemographic characteristics were intervened with HIIT exercise due to the scarce existing scientific evidence. The PRISMA declaration criteria were used to filter the cynical trials, with the aim of analyzing those that met the objective of this systematic review. On the other hand, questions were formulated using the PICO strategy (P: oncological patients during or after antineoplastic treatment; I: high intensity training; C: patients who did not receive high intensity exercise intervention; O: effects of high intensity training on cardiovascular health, toxicity and cardiovascular risk in oncological patients) (Santos C. et al. 2007).

The methodological evaluation was carried out under the PEDro (*Physiotherapy Evidence Database*) scale (Maher C. et al. 2003) which is a tool that allows the methodological validation of clinical trials, consisting of 11 items where it is rated if the study had choice criteria, the subjects were randomized, if the groups compared are similar, both the subjects and the therapists and evaluators are blinded, the measures are obtained in more than 85% of the subjects, the results presented are from all subjects as well as statistical comparisons and that they provide punctual measures. This scale is based on the Delphi list developed by Verhagen, et al. (1998) and assigns values of 1 or 0 points according to whether or not it complies with the item to be evaluated. With respect to this evaluation, it was carried out by the researchers I. S-G; HE. R-L. and M. D-B. checked the data and in case of a final deference of more than 2 points or a tie between the evaluators on the result, a new evaluator (J. P-R) will

carry out a new review to obtain the final result.

Randomized clinical trials were analyzed in oncology patients with cardiotoxicity or with risk factors that could generate it, with different types of cancer, age and sex. Regarding the publication date of the studies, these were from 2018 to 2020 in Spanish or English. Studies that addressed patients with metastasis or any contraindication for the execution of exercise; research not indexed in the mentioned databases, gray literature (books, theses and degree works) and studies performed on animals were excluded. In addition, we filtered out those studies that after evaluation of the title, abstract and key words did not meet the acceptance criteria, as well as inconclusive studies that did not meet the research objective and did not respond to our research question.

RESULTS

In the first instance, 852 titles of clinical studies related to exercise and cancer were recruited in the previously mentioned databases and 560 articles were selected, but only 193 studies remained according to the interval of the year of publication, books, theses and animal model that were eliminated. Subsequently, 180 articles were removed by performing a full-title and research methodology analysis, leaving 13 remaining. After a full-text analysis, 9 papers were selected (Pereira J. et al. 2022; Kesting S. et al. 2022; Ansund J. et al. 2021; Lee K. et al. 2021; Bell R. et al. 2021; Toohey K. et al. 2020; Lee K., 2020; Lee K., 2019; Lee K., 2019) (Figure 1) that answered our research question; which were assessed using the PEDro scale (Table 1) and then summarized in detail to understand and capture their main characteristics (Table 2).

The studies collected addressed a total of 724 patients mainly with breast cancer (Pereira J. et al. 2022; Ansund J. et al. 2021; Lee K. et al. 2021; Lee K. et al. 2020; Lee K. et al. 2019; Lee K. et al. 2019; Lee K. et al. 2019), prostate (Pereira J. et al. 2022), childhood cancer (Kesting S. et al. 2022), among other cancers with different etiology (Bell R. et al. 2021; Toohey K. et al. 2020), in terms

of staging stage I-II prevailed, participants were under neo or adjuvant, or post chemotherapeutic treatment (anthracyclines, taxanes or a combination of both).

The duration of the interventions ranged from 36 (Pereira J. et al. 2022), 32 (Ansund J. et al. 2021), 24 (Bell R. et al. 2021; Lee K., 2020), 16 (Lee K. et al. 2021; Lee K., 2019) and even single session (Kesting S. et al. 2022) HIIT training. The tests were before and after intervention (Pereira J. et al. 2022; Kesting S. et al. 2022; Ansund J. et al. 2021; Lee K. et al. 2021; Bell R. et al. 2021; Toohey K. et al. 2020; Lee K., 2020; Lee K., 2019; Lee K., 2019), 2 to 4 days before the intervention and 2 to 4 days after the last session (Toohey K. et al. 2020), even after 1 and 2 years of follow-up (Ansund J. et al. 2021). The time of the sessions varied according to the training schedule, some were extensive 50-60 minutes[20] and others shorter 20-30 minutes (Toohey K. et al. 2020) which depended on the structure of the training. It should be noted that the interdisciplinary team was present in all the interventions and Table 2 shows all the detailed characteristics of each study.

In the evidence found, it is notable that cardiac toxicity may be the second leading cause of mortality and morbidity in breast cancer patients, and even the death rate is twice as high compared to people of the same age (Ansund J. et al. 2021). There is also a deterioration in cardiorespiratory fitness (~10%) after anthracycline-based chemotherapy and this is unlikely to increase or improve over the years despite completion of treatment (Abarzúa J. et al. 2019). VO2 is reduced by 5 to 26% during anthracycline chemotherapy and it is very difficult to recover their initial cardiorespiratory condition after treatment. In one study after one year in the control group there was a decrease in VO2 of 3%, compared to a 9% increase in participants approached with HIIT exercise (Ansund J. et al. 2021).

On the other hand, from the cardiovascular point of view, it was determined that high-intensity interval training - HIIT - improves ejection fraction (39.6±7.3 vs. 46.5±2.4; p= 0.005) (Pereira J. et al. 2022; Lee K. et al. 2021),

maximum heart rate (154.0±13.0 vs 168.5±8.0; *p*= 0.005) (Pereira J. et al. 2022; Kesting S. et. al. 2022), systolic blood pressure (133.5±6.2 vs 122.0±1.6; *p*= 0.005) and diastolic blood pressure (86.5±10.3 vs 81.0±2.4; *p*= 0.005) (Pereira J. et al. 2022). In addition, it increases vo2 levels (Pereira J. et al. 2022; Ansund J. et al. 2021; Toohey K. et al. 2020; Lee K. 2020; Lee K. et al. 2019), after a training program. In addition, it improved other variables such as results in the 6-minute walk test (Pereira J. et al. 2022; Lee K. et al. 2021; Lee K. et al. 2020; Lee K. et al. 2019; Lee K. et al. 2019), stress test (Pereira J. et al. 2022), anthropometry (Pereira J. et al. 2022; Kesting S. 2022; Bell R. et al. 2021), quality of life (Pereira J. et al. 2022; Lee K. et al. 2021; Lee K. et al. 2020; Lee K. et al. 2019; Lee K. et al. 2019), fatigue with the Borg scale (Pereira J. et al. 2022; Lee K. et al. 2021; Toohey K. et al. 2020; Lee K. et al. 2020; Lee K. et al. 2019; Lee K. et al. 2019), sarcopenia (Pereira J. et al. 2022), clinical parameters (Pereira J. et al. 2022; Kesting S. et al. 2022; Ansund J. et al. 2021; Bell R. et al. 2021), hemodynamic (Pereira J. et al. 2022; Ansund J. et al. 2021; Bell R. et al. 2021), sedentary and physical activity status by accelerometer (Pereira J. et al. 2022; Bell R. et al. 2021), physical function with the get-up-and-go (TUG) test(Lee K. et al. 2021; Lee K. et al. 2020), 30-second sit and stand test (30STS))(Lee K. et al. 2021; Lee K. et al. 2020; Lee K. et al. 2019), Margarita-Kalamen stair climbing test (Lee K. et al. 2021; Lee K. et al. 2020; Lee K. et al. 2019), saliva collection and analysis with IPRO *Oral Fluid Collection* Kits (Lee K. et al. 2020) (*p*= 0.005).

Finally, collecting the information from the studies analyzed in this research, we also managed to demonstrate that both HIIT training and the modality of continuous moderate intensity training (MICT) obtained good results, but the former seems to indicate more remarkable benefits (Pereira J. et al. 2022; Bell R. et al. 2021; Toohey K. et al. 2020), significantly improving VO_2 (Ansund J. et al. 2021; Bell R. et al. 2021; Lee K. et al. 2019), reducing of inflammation by biomarkers that potentiate cardiovascular disease[22] , improving patients' quality of life (Lee K. et al. 2021), vascular endothelial function and maintaining wall

thickness (Lee K. et al. 2019), being a long-term cardioprotective mechanism (Ansund J. et al. 2021; Toohey K. et al. 2021; Lee K. et al. 2021), safe and effective in cardio-oncology patients.

DISCUSSION

This research consolidates the safety and efficacy of HIIT training in the cardio-oncology patient, in addition to the notorious benefits it demonstrates in this type of population. The selected clinical trials have a diversity of items assessed and examined in comparison with older studies, supporting the benefits of high-intensity exercise in cardiovascular toxicity or in oncology patients at risk of cardiotoxicity.

In 2016 the work of Nandini, et al. (2016) collected analyzed studies of small groups of patients who were under antineoplastic treatment for breast cancer mainly, presenting outstanding results in the increase of Vo_2 , decrease of heart rate and blood pressure. In the same year, Toohey, et al. (2017) approached 24 cancer survivors, assigning them in a HIIT training group, which consisted of a warm-up (5 min) + workout (7 × 30 s intervals ≥85% Fc max) + cool-down, while the MICT group performed continuous training for 20 min (≤55% Fc max), for 12 weeks. Both interventions obtained significant improvements, although the group that performed HIIT stood out for higher levels of health and reduction of cardiovascular disease risk factors. Both studies go hand in hand with the results presented in this systematic review, where HIIT improves different physical, cardiovascular and metabolic variables.

On the other hand, the study by Von, et al. (2016) in a young amateur triathlete diagnosed with acute myeloid leukemia undergoing chemotherapy and stem cell transplantation, who presented heart failure with an LVEF <55%, to whom HIIT training (swimming, walking and cycling) was applied, for 3 years improved athletic performance, the workload doubled, as well as the maximum oxygen consumption and although the LVEF remained unchanged, it was shown that exercise is safe despite cardiac toxicity. Highlighting that, in our collected studies LVEF levels did manage to increase with high intensity training (Pereira J. et al.

2022; Lee K. et al. 2021) this finding is of particular relevance, as decreased LVEF has been identified as a key predictor of cardiovascular events in cancer patients treated with chemotherapy (Plana JC. et al. 2014).

Now, the observed improvement in cardiac function in the patients in our review could be attributed to the ability of HIIT to modulate cardiovascular risk factors, including lowering blood pressure, improving insulin resistance, and optimizing lipid profile (Lavie CJ. et al. 2015; Adams S. et al. 2017). These systemic effects, combined with the ability of high-intensity exercise to induce beneficial physiological adaptations in the heart, position HIIT as a comprehensive strategy to counter cardiovascular toxicity in oncology patients.

Likewise, Adams, et al. (2017) in their study with 63 testicular cancer survivor patients, approached for 12 weeks with: warm-up + training (4 intervals of 4 min each, progressing from 75% to 95% of peak VO2 and active recovery of 3 min of 5%-10% of VO2) + cool-down 5 min. They determined that HIIT significantly improved VO2, representing a reversal of almost a decade of cardiorespiratory aging; because, each optimization of 3.5 ml O2/kg/minute in peak VO2 is associated with a reduction in the relative risk of overall mortality between 10% to 25%. These results and those presented in the present investigation, also manage to agree with those published by Meneses J. et al. in 2015 and Nakoto et al. in 2018 who managed to demonstrate that exercise is a strategy that can mitigate cardiovascular repercussions and cancer semiology.

STUDY LIMITATIONS

Despite the significant advances outlined in this review, it is imperative to recognize the inherent limitations of the included studies, such as variability in training protocols and heterogeneous study populations. Future research should address these limitations and focus on

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optimizing HIIT programs to suit the specific needs of cancer patients.

CONCLUSION

The evidence accumulated throughout this systematic review consistently supports the benefits of high-intensity interval interval training (HIIT) in improving various cardiovascular variables in cancer patients. Our comprehensive analysis of the literature has revealed that HIIT not only leads to significant improvements in functional capacity and quality of life, but also emerges as a potentially promising strategy to prevent cardiotoxicity associated with antineoplastic therapies. In particular, we observed a substantial increase in left ventricular ejection fraction (LVEF) levels in those patients undergoing HIIT, suggesting potential protection against ventricular dysfunction, which is a complication commonly associated with oncologic therapy.

A hypothesis could be put forward for future research, showing that HIIT training not only improves cardiovascular health in cancer patients, but could also play a key role in the prevention of cardiotoxicity associated with antineoplastic therapy. The findings presented in this systematic review open new perspectives in the comprehensive care of oncology patients, providing a solid basis for the implementation of personalized exercise strategies that not only combat the physical burden of disease, but also safeguard cardiovascular health effectively. But we also emphasize that the prescription of this type of training should be individualized, progressive and under the supervision of health professionals trained in this type of treatment.

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Figure 1. PRISMA flow diagram

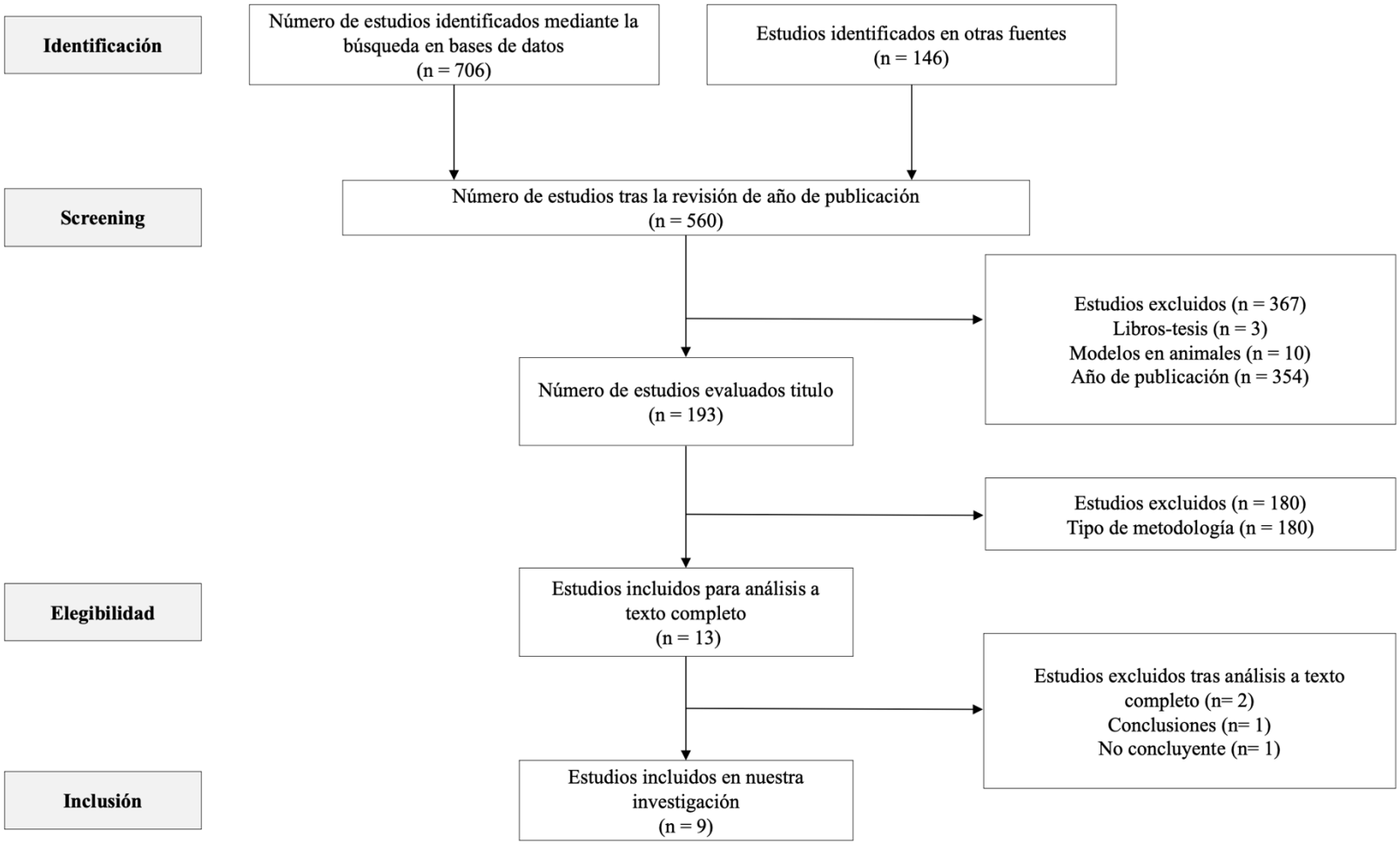

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Table 1. PEDro scale for the evaluation of the methodological quality of the studies included in the review (*n = 9)*.

Reference	*P1*	*P2*	*P3*	*P4*	*P5*	*P6*	*P7*	*P8*	*P9*	*P10*	*P11*	*Total*
Pereira J, et al.[16]	+	+	+	+	-	-	+	+	+	+	+	8
Kesting S, et al.[17]	+	-	-	-	-	-	-	+	+	-	+	3
Ansund J, et al.[18]	+	+	+	+	-	-	+	+	+	+	+	8
Lee K, et al.[19]	+	+	-	+	-	-	-	+	+	+	+	6
Bell R, et al.[20]	+	+	+	+	+	-	-	+	+	+	+	8
Toohey K, et al.[21]	+	+	+	+	+	+	+	+	+	+	+	10
Lee K, Dieli C.[22]	+	+	+	+	+	-	+	+	+	+	+	9
Lee K, et al.[23]	+	+	+	+	+	-	+	+	+	+	+	9
Lee K, et al.[24]	+	+	-	+	-	-	-	+	+	+	+	6

PEDro (Physiotherapy Evidence Database): + Yes; - No.

P1: Choice criteria; P2: Random assignment; P3: Allocation concealment; P4: Similar groups at baseline; P5: Blinding of participants; P6: Blinding of therapists; P7: Blinding of evaluator; P8: Dropouts < 15%; P9: Intention-to-treat analysis; P10: Reported differences between groups; P11: Point estimates and reported variability.

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Table 2. Characteristics of the experimental studies (*n = 9*).

Author	*n*	*Age*	*Features*	*Groups and techniques*	*Intervention*	*Weather*	*Conclusions*
Pereira J, et al.[16] 2022 (Colombia).	465	-	Patients with stage II breast or prostate cancer	Strength + MICT Strength + HIIT G. Control	Strength + MICT Group: Aerobic exercise (60-80%) + Strength (40-60%) Strength + HIIT Group: 30-30 (60-80 and 80-90%) + strength (40-60%)	36 sessions	HIIT training outperformed the MICT group and the MICT group outperformed the control group. Improved Vo2, muscle strength, decreased sarcopenia, depression and anxiety.
Kesting S, et al.[17] 2022 (Germany).	14	13.9	Patients diagnosed with infantile CA, had a central venous catheter planned or implanted, signed consent and legal guardians and treating physician, without presence of bone tumors.	HIIT Group	10 intervals of 15 seconds at algae intensity (>90% Fcmax) followed by one minute of active recovery.	1 session	The HIIT protocol is not suitable for most children during the first few weeks of cancer treatment, it is feasible and safe for patients who suffer only mild side effects from treatment.
Ansund J, et al.[18] 2021 (Sweden).	88	18-70	Patients with a diagnosis of stage I-III breast cancer who underwent chemotherapy (anthracyclines, taxanes or a combination of these).	Group RT-HIIT AT-HIIT Group UC Group.	RT-HIIT: resistance training (8 to 12 repetitions at 75 to 80% of 1RM) + 3 sets of 3 minutes of high intensity interval aerobic training (HIIT). AT-HIIT: 20 min moderate MICT + HIIT performed by the RT-HIIT group.	16 weeks	At 1 year, plasma Nt-pro-BNP was significantly lower in the exercise groups compared to the UC group. At 2 years there was a significant drop in VO2 (3%) compared to HIIT patients, which increased to 9%. HIIT is related as a long-term cardioprotective mechanism in breast cancer patients.

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Lee K, et al.[19] 2021 (Los Angeles, California).	30	46.9	Women >18 years with stage I-II breast cancer, neo or adjuvant anthracycline treatment, start of training protocol 1 or 2 weeks starting chemotherapy.	HIIT Group Group CON	5 min warm up (10 % PPO) + HIIT (7 intervals of 1 min performed at 90 % PPO followed by a 2 min interval performed at 10 % PPO) of 20 min (90 % PPO/10 % PPO) + 5 min cool down.	8 weeks	The HIIT group improved cardiorespiratory functionality, being an effective strategy to improve physical function and maintain quality of life in breast cancer patients undergoing anthracycline-based chemotherapy.
Bell R, et al.[20] 2021 (New Zealand).	20	30-60	Patients who have completed primary treatment (chemotherapy and/or radiotherapy) and who have completed low/moderate intensity training.	HIIT Group MICT Group	HIIT: In the first two weeks, warm-up (3 min) + training (4 intervals of 2 min at 70-75% FCmax, 2 min active recovery <60% Fcmax) + 5 min active cool-down. MICT: In the first two weeks, warm-up + 14 min of stationary cycling at 60% Fcmax was performed, increasing to 25 min + cool-down.	12 weeks	Increased VO2 in breast cancer survivors, and aerobic capacity, progression from moderate to higher intensity exercise reaches a "threshold" that is not reached in low intensity exercise. HIIT is not shown to be superior to MICT, however, the long-term effects of HIIT are estimated to be remarkable to other interventions.
Toohey K, et al.[21] 2020 (Australia).	17	50-75	Sedentary patients two years of antineoplastic treatment, not medicated for blood pressure, free of metastases, with capacity to perform exercise on stationary ergometric bicycle.	HIIT Group. CMIT Group. Group CON.	In all groups, heating and cooling was performed in cycloergometers at ~ 50% of their maximum power (watts). HIIT: 7 intervals of 30 seconds at high intensity and 2 minutes of active recovery. CMIT: pedaling for 30 min, of which 20 min were performed at 55-65% of your HRmax.	12 weeks	HIIT training improved cardiovascular fitness in contrast to CMIT and the control group, improved cardiac regulation and sympathetic nervous system responses, indicating reduced risk of heart disease. High-intensity interval training was safe and effective.

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Lee and Dieli.[22] 2020 (Los Angeles California)	30	46.9	Patients diagnosed with stage I-III breast cancer, in neo or adjuvant chemotherapeutic treatment with anthracyclines, start of training 1 or 2 weeks after chemotherapy initiation.	HIIT Group Group CON	5 min warm up (10 % PPO) + HIIT (7 intervals of 1 min performed at 90 % PPO followed by a 2 min interval performed at 10 % PPO) of 20 min (90 % PPO/10 % PPO) + 5 min cool down.	8 weeks	Circulating levels of hsCRP were maintained in the HIIT group, generating a reduction in cardiovascular inflammation. It is a safe and feasible intervention for breast cancer patients.
Lee K, et al.[23] 2019 (Los Angeles, California).	30	46.9	Patients diagnosed with stage I-III breast cancer, in neo or adjuvant chemotherapeutic treatment with anthracyclines, start of training 1 or 2 weeks after initiation of chemotherapy.	HIIT Group Group CON	5 min warm up (10 % PPO) + HIIT (7 intervals of 1 min performed at 90 % PPO followed by a 2 min interval performed at 10 % PPO) of 20 min (90 % PPO/10 % PPO) + 5 min cool down.	8 weeks	The HIIT group maintained VO2 max, and the CON group showed a decline. The study supports the use of a short-term HIIT intervention as an option to maintain cardiorespiratory fitness during anthracycline chemotherapy.
Lee K, et al.[24] 2019 (Los Angeles, California).	30	46.9	Patients with stage I-III breast cancer, undergoing chemotherapy treatment with anthracyclines, start of training 1 or 2 weeks after initiation of chemotherapy.	HIIT Group Group CON	5 min warm-up (10 % PPO) + HIIT (7 intervals of 1 min performed at 90 % PPO followed by a 2 min interval performed at 10 % PPO) of 20 min (90 % PPO/10 % PPO) + 5 min cool down.	8 weeks	After the intervention, FMDba significantly increased and cIMT levels were maintained in the HIIT group, contrary to the CON group. This is the first study to demonstrate improvement in vascular endothelial function and maintenance of wall thickness.

MICT: moderate-intensity continuous training; HIIT: high-intensity interval training; HRmax: maximum heart rate; RT-HIIT: resistance and high-intensity interval training; AT-HIIT: moderate-intensity aerobic and high-intensity interval training; UC: usual care; cTnT: plasma cardiac troponins; NT-pro-BNP: natriuretic peptide, used in the diagnosis and assessment of heart failure; VO2: volume of oxygen; CON: control group; PC6M: 6-minute walk test; hsCRP: circulating levels of high-sensitivity C-reactive protein; PPO: peak power output.

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