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Effects of high intensity interval training in cancer patients newly diagnosed with cardiovascular disease

Efectos del entrenamiento interválico de alta intensidad en pacientes con cáncer con nuevo diagnóstico de enfermedad cardiovascular

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Keywords: high-intensity interval training, exercise, cancer, cardiovascular disease.

Palabras clave: *entrenamiento interválico de alta intensidad, ejercicio, cáncer, enfermedad cardiovascular.*

ABSTRACT

Introduction: cancer and cardiovascular diseases (CVD) are among the main causes of mortality worldwide. In CVD patients, continuous moderate-intensity training and High-Intensity Interval Training (HIIT) are safe, effective, and may be a strategy to improve cardiovascular health. **Material and methods:** a prospective experimental study was performed with a sample of 275 cancer survivors recently diagnosed with CVD and low functional capacity, less than 4 METs (metabolic equivalent of task). A training program lasting 36 weeks was applied with assistance three times a week of 70 minutes per intervention and with pre and post-measurements of anthropometry by bioimpedance, New York Heart Association (NYHA) Scale, stress test, echocardiogram, sarcopenia (Anthropometry, muscular strength, and functionality), lipid profile, quality of life European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTG-C30), questionnaire for fatigue (FACT-Fatigue scale), 6 minutes walk test for distance traveled and estimated VO_2. **Results:** significant improvement was reported in ejection fraction (40 ± 4.8 vs 47 ± 5.6; $p \leq 0.05$), functional capacity reported in METs (2.1 ± 1.6 vs 3.9 ± 0.9), quality of life (108 ± 14 vs 121 ±7.6; p = 0.002) and improvement in estimated VO_2max, strength, muscle percentage, and post-intervention blood pressure ($p \leq 0.05$). In addition, the lipid profile, glucose, abdominal circumference, fat percentage ($p \leq 0.05$), and sarcopenia (32 vs 13%; p = 0.012) decreased after HIIT training without any adverse events during the interventions in the study population. **Conclusions:** the use of HIIT training is an efficient and safe way to improve physical capacity, quality of life, anthropometric parameters, and control cardiovascular risk factors (CVRF) in cancer survivors with a recent diagnosis of CVD.

RESUMEN

Introducción: *el cáncer y las enfermedades cardiovasculares (ECV) se encuentran entre las principales causas de mortalidad a nivel mundial. En pacientes con ECV, el entrenamiento continuo de intensidad moderada y el entrenamiento en intervalos de alta intensidad (HIIT) son seguros, eficaces y pueden ser una estrategia para mejorar la salud cardiovascular.* ***Material y métodos:*** *estudio experimental prospectivo con una muestra de 275 supervivientes de cáncer con diagnóstico reciente de ECV y baja capacidad funcional, menos de 4 METs (equivalente metabólico). Se aplicó un programa de entrenamiento con duración de 36 semanas con asistencia tres veces por semana de 70 minutos por intervención y con mediciones pre y post de antropometría por bioimpedancia, escala de la New York Association, prueba de esfuerzo, ecocardiograma, sarcopenia (antropometría, fuerza y funcionalidad muscular), perfil lipídico, calidad de vida (EORTG-C30), cuestionario de fatiga (escala FACT-Fatigue), prueba de caminata de 6 minutos para distancia recorrida y VO2 estimado.* ***Resultados:*** *se reportó mejoría significativa en la fracción de eyección del ventrículo izquierdo (40 ± 4.8 vs 47 ± 5.6; p ≤ 0,05), capacidad funcional reportada en METs (2.1 ± 1.6 vs 3.9 ± 0.9), calidad de vida (108 ± 14 vs 121 ± 7.6; p = 0.002) y mejora en el VO2 máx, fuerza, porcentaje muscular y presión arterial postintervención (p ≤ 0.05). Además, el perfil lipídico, la glucosa, la circunferencia abdominal, el porcentaje de grasa (p ≤ 0.05) y la sarcopenia (32 vs 13%; p = 0.012) disminuyeron después del entrenamiento HIIT sin ningún evento adverso durante las intervenciones en la población de estudio.* ***Conclusiones:*** *el uso del entrenamiento HIIT es una forma eficiente y segura de mejorar la capacidad física, la calidad de vida, los parámetros antropométricos y el control de los factores de riesgo cardiovascular (FRCV) en supervivientes de cáncer con diagnóstico reciente de ECV.*

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Abbreviations:

1RM = One repetition maximum.
AHA = American Heart Association.
ACS = American Cancer Society.
AMPK = 5′ adenosine monophosphate-activated protein kinase.
BMI = Body mass index.
BPM = Beats per minute.
CaMK = Calcium-calmodulin-dependent protein kinase kinase.
CORE = Cardio-oncology rehabilitation.
CR = Cardiac rehabilitation.
CRF = Cardiorespiratory fitness.
CV = Cardiovascular.
CVD = Cardiovascular diseases.
CVRF = Cardiovascular risk factors.
DBP = Diastolic blood pressure.
EORTC-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.
HIIT = High-Intensity Interval Training.
LDL and HDL = Low and high-density lipoproteins.
LVEF = Left Ventricular Ejection Fraction.
METs = Metabolic equivalent of task.
MHR = Maximal Heart Rate.
NYHA = New York Heart Association.
PGC-1 = Peroxisome proliferator-activated receptor gamma coactivator 1-alpha.
QoL = Quality of life.
SBP = Systolic blood pressure.
VO_2 = Estimated Maximal Oxygen Uptake.

INTRODUCTION

Cancer and Cardiovascular Disease (CVD) are among the leading causes of mortality worldwide.[1] Emerging epidemiological evidence demonstrates the entwined relationship between common etiologies and risk factors between cancer and CVD.[2] In recent times, it has been demonstrated that oncological survivors of most site-specific cancers have increased their risk in the medium-term to long-term compared with the general population.[3] Also, common anti-oncological therapies can be directly injurious to the cardiovascular (CV) system,[4] leading to significantly increased risks for acute and long-term CVD in survivors.[5] This brings the need for more strategies that could reduce the incidence and severity of these associated risk factors within both conditions. Cardiac rehabilitation (CR) has been the cornerstone of primary and secondary CVD treatment for decades. Recently, The American Heart Association (AHA) and the American Cancer Society (ACS) endorsed the adoption of the CR model to improve CVD outcomes in cancer patients and survivors.[6]

Added to the higher risk of CVD and other comorbidities, oncological survivors have a decline in quality of life (QoL) because of the long-term effects of some oncological treatments (surgery, chemotherapy, radiotherapy, hormonal therapy) and the treatment-related adverse effects such as fatigue, pain, decreased activity levels that impair physical capacity, muscle strength, cardiorespiratory fitness, range of motion limitations, lymphedema, and limb dysfunction.[7,8]

Exercise has clearly demonstrated to be a strong pleiotropic intervention with established multi-system benefits in non-cancer populations.[9] These benefits of exercise for oncological survivors have been clearly demonstrated, including improved Cardiorespiratory Fitness capacity (CRF),[10] muscular strength,[11] long-term symptoms (i.e., fatigue, pain),[12] and psychosocial well-being of survivors (i.e., anxiety and depression).[13]

The association between exercise and decreased mortality has led to the investigation of different intervention strategies in cancer patients,[14] including resistance exercises that begin to play a very important role in cancer patients. Concerning High-Intensity Interval Training (HIIT) is a variable-intensity resistance modality that is characterized by having very short periods with high-intensity workloads, which are interspersed by rest or periods at low intensity as recovery.[15] However, as it is a more intense modality for patients, it is not always the first choice for physical exercise, and therefore, the patient must be selected, and this modality must be prescribed carefully and under strict monitoring to ensure the safety of the participants.

HIIT has been shown to be time efficient due to the total time of vigorous exercise is greater than what could be achieved in a continuous exercise session with the same intensity before exhaustion, as well as being a safe option to improve CRF, which is measured by the

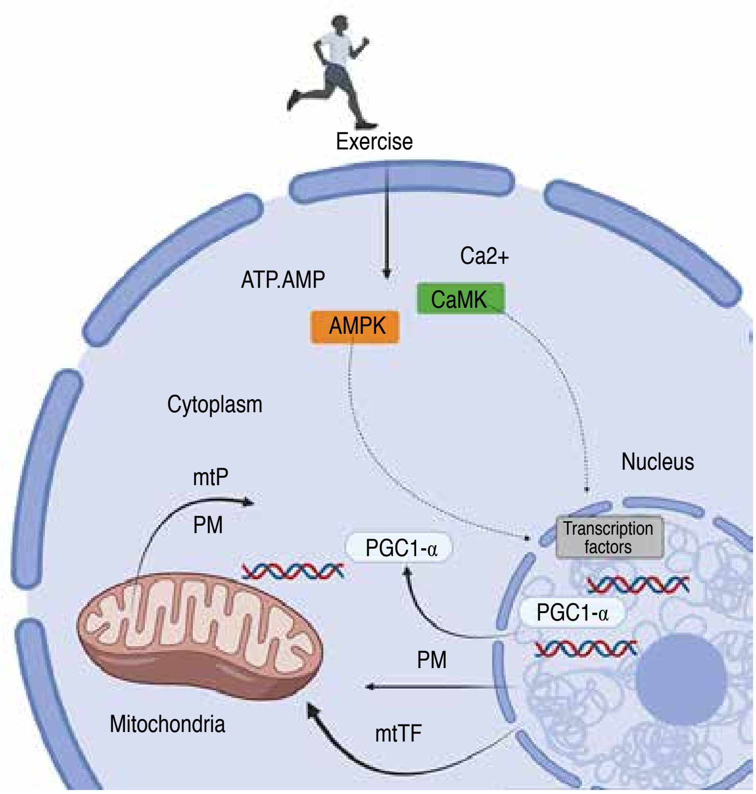

Figure 1: Regulation of mitochondrial biogenesis by HIIT training. 1) During endurance activity, an acute increase in the intracellular concentration of Ca+, ADP, and AMP and a decrease in the concentration of glycogen in contracting muscles is observed. High concentrations of ADP and AMP induce phosphorylation of AMPK, while high concentration of Ca+ causes autophosphorylation of CaMK through the protein calmodulin. This dual activation of AMPK and CaMK regulates transcription factors that modulate PGC-1alpha gene expression, a crucial step in the regulation of mitochondrial biogenesis. 2) AMPK, p38, Gen5, and siRNA, as kinases and acetylation modulators, carry out the phosphorylation and deacetylation of PGC-1a, thus enhancing its activity. 3) The activated form of PGC-1a associates with chromatin regulatory factors, triggering the opening of chromatin to facilitate transcription. Furthermore, PGC-1a establishes interactions with other transcription factors, such as NRF. 4) This process results in an increase in the expression of mitochondrial proteins, as well as the expression of mitochondrial transcription and replication factors (mtTFs) encoded in DNA. 5) Once expressed, mtTFs migrate to the mitochondria, bind to mitochondrial DNA (mtDNA), and catalyze the expression of mtDNA-encoded proteins (mtP), as well as mtDNA replication. Finally, both mtTF and mtP form mature complexes, triggering mitochondrial division and resulting in the formation of new mitochondria. Created with BioRender.com

AMP = adenosine monophosphate. AMPK = 5' adenosine monophosphate-activated protein kinase. AMP-activated protein kinase. ATP = adenosine triphosphate. CaMK = Calcium-calmodulin-dependent protein kinase kinase. PGC-1 = Peroxisome proliferator-activated receptor gamma coactivator 1-alpha. PM = mitochondrial proteins.

maximum oxygen consumption (VO_2max).[8] In addition, its activation effects on AMPK and Calcium-calmodulin-dependent protein kinase kinase (CaMK) pathways increase the activity of PGC-1 alpha and thus improve mitochondrial biogenesis *(Figure 1)*. For this reason, it is posed as a research question: what are the cardiovascular effects of HIIT in cancer patients newly diagnosed with CVD? Therefore, the objective is to identify the cardiovascular effects of high-intensity interval training in cancer patients with the diagnosis of cardiotoxicity.

Physical exercise is a therapeutic strategy that has the ability to act through multiple systems, facilitating the attenuation and prevention of side effects associated with treatments. Until now, exercise recommendations for cancer patients have been focused primarily on low-to-moderate intensity aerobic activity. However, it is currently suggested that high-intensity exercise prescription has the same and even greater effects compared to continuous aerobic exercise and that this could reduce the risk of mortality in cancer.

In patients with CVD, moderate-intensity continuous training and HIIT are both safe and effective in improving CV health.[16] However, HIIT is associated with a greater frequency and magnitude of benefits in the CV function (i.e., increased CRF,[17] CVD risk factors,[18] QoL,[19] and CV morbidity and mortality.[17] For this reason, we may estimate the effects (CV parameters and QoL) of HIIT on oncological survivors newly diagnosed with CVD with low functional capacity.

MATERIAL AND METHODS

Study design

A prospective experimental study was performed with a sample of 275 cancer survivors (stage II cancer) referred by the oncology department who were recently diagnosed with CVD and low functional capacity (less than 4 METs). Participants shared similar in terms of Left Ventricular Ejection Fraction (LVEF), functional fitness capacity (CRF) by New York Heart Association (NYHA) and stress test, percentage of both muscle mass and body fat, and body mass index (BMI), abdominal circumference, and cardiovascular risk factors (CVRF) such as diabetes, hypertension, and dyslipidemia.

Participants

In the present investigation, patients were referred by the oncology service who were newly diagnosed with CVD after their anti-oncological treatment program in Cúcuta, Colombia. The diagnosis of CVD was made with the new onset of CV symptoms, abnormal natriuretic peptides, positive troponin, or decreased LVEF. Patients were referred after one month of the completion of their oncological treatment.

Inclusion and exclusion criteria

Regarding inclusion criteria, the patients had to be in stage II of their oncological process and sign the respective informed consent, that they could attend cardiovascular rehabilitation sessions three times a week, and finally, that they had an LVEF greater than 35% and who were over 18 years of age. Contraindications included those who presented severe pain in both lower and upper limbs; a heart rate above 120 beats per minute (BPM) at rest; patients with moderate or high functional capacity (> 4 METs), systolic blood pressure (SBP) > 190 mmHg or diastolic blood pressure (DBP) > 120 mmHg; unstable angina; people who presented a contraindication for make exercise training and finally those who showed hemodynamic instability without improvement in any test or during the intervention process.

Table 1: Types of cancer. (N = 275).

Types of cancer	Experimental group n (%)
Prostate	82 (29.8)
Breast	70 (25.4)
Colorectal	27 (9.8)
Cervix	13 (4.7)
Thyroid	22 (8.0)
Lung	22 (8.0)
Stomach	13 (4.7)
Liver	8 (2.9)
Pancreas	3 (1.0)
Kidney	13 (4.7)
Esophagus	2 (0.72)

Ethical considerations

This clinical study was carried out following the Declaration of Helsinki, the signing of the informed consent, under the authorization of the subjects involved, and the ethics committee of the Centro de Estudios e Investigación FISICOL with code IP245.

Variables

The anthropometric characteristics data such as weight, height, body mass index, abdominal circumference, percentages of body fat, and muscle mass were collected by bioimpedance. In addition to this, through a questionnaire (created for this research), personal and family history information was obtained.

The clinical and hemodynamic parameters were considered levels of cholesterol, triglycerides, and low and high-density lipoproteins (LDL and HDL) through a blood glucose sample. A two-dimensional echocardiography was also performed to obtain the LVEF and analyze movements in real-time; with this, the New York Heart Association (NYHA) classification was identified in each subject, the perceived dyspnea and the effort was measured using the modified Rating of Perceived Exertion (RPE) by the modified Borg scale,[20] in terms of heart rate, a Polar Multisport RS800CX system monitored it, blood pressure taken manually and oximetry with a portable oximeter.

Regarding the QoL, it was measurable thanks to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTG-C30)[21] Questionnaire was used with its respective interpretation following the guide of the manual of the European Organization for Research and Treatment of Cancer[22] that consists of 30 questions, with a score of 1-4 items, the higher the score, the better the quality of life. Likewise, the levels of sarcopenia were determined. Where the three criteria of the European Consensus on Sarcopenia[23] in 2010 are as follows: a) Walking, using the

Table 2: Baseline characteristics of the study population. (N = 275).

Characteristics	Experimental group
Sex	
Men	150
Woman	125
Age (years)	56 ± 10
LVEF, (%)	40 ± 4.8
Size, (m)	1.63 ± 14
Weight, (kg)	84 ± 10.7
BMI	34 ± 3.1
Abdominal circumference, (cm)	93 ± 7.5
Fat*	29 ± 4.4
Muscle*	32 ± 9.1
Force, (kg)	27 ± 9.3
Sarcopenia*	32%
Calf circumference	37.9 ± 11.5
Cholesterol, (mg/dL)	195 ± 13.5
Triglycerides, (mg/dL)	130 ± 12.7
LDL, (mg/dL)	118 ± 23.4
HDL, (mg/dL)	41 ± 3.6
Fasting glucose, (mg/dL)	135 ± 11.3
Estimated VO_2	7.5 ± 5.7
METs	2.1 ± 1.6
Fatigue (FACT-F)	16.3 ± 9.7
Quality of life	108 ± 14.0
Distance traveled	243 ± 23.0
MHR in stress test	156 ± 12.0
Overweight and/or obesity*	78
Abdominal obesity*	88
Dyslipidemia*	25
Arterial hypertension*	31
Diabetes mellitus*	56
Renal disease*	11
Sedentary lifestyle*,‡	91
Depression*	57
Anxiety*	18
Smoking*	40
Alcoholism*	15
Improper diet*	56
MI history*	4
Sex female*	45
Age,*,§	5

FACT-F = functional assessment of cancer therapy fatigue. mg/dL = milligrams/deciliters. METs = metabolic equivalent. MHR = maximum heart rate.
* Percentage. ‡ Less than 150 minutes per week. § Over 60 years old.

short physical performance battery (SPPB). b) Muscular strength is measured using dynamometry with values dependent on sex and age. c) Muscle mass, measured with BMI and calf circumference, as a starting point of 31 cm. Finally, fatigue was evaluated according to the Fatigue Scale for Functional Evaluation of Cancer Therapy (FACT-Fatigue scale),[24] which consists of 13 items with a score of 0-4 each, with a higher score reflecting less fatigue associated with cancer.

On the other hand, for the estimated volume of oxygen, a 6-minute walk test (6MWT)[25,26] was performed, the same for meters traveled, VO2 (Estimated Maximal Oxygen Uptake), METs (Metabolic Equivalent of Task), to obtain exact and measurable values of the physical and aerobic capacity accordance with the American Thoracic Society (ATS) Statement: Guidelines for the six-minute walk test of the ATS.[25,26]

Interventions

Firstly, every participant was evaluated by the cardiac rehabilitation department to determine his baseline clinical status and sociodemographic, anthropometric, and physiological characteristics. We performed an Exercise Stress Test through Naughton's protocol for Maximal Heart Rate (MHR) and were able to prescribe exercise effectively and accurately. Regarding the tool to measure strength, the one repetition maximum (1RM) test was used. It is worth mentioning that, during the intervention, the participants received counseling regarding stopping smoking and nutritional support to further improve patient outcomes as the standard of care in the CRP.

The training program lasted 36 weeks with assistance three times a week with 70 minutes per intervention, where 10 minutes were warm-up (breathing exercises, walking, stretching), 20 minutes of strength training, and 30 minutes of aerobic exercise consisted of a protocol created for this experimental group that we call it 30-30. Thirty seconds at moderate intensity (60-80% of MHR obtained by stress test) and 30 seconds at a high intensity (80-90% of MHR obtained by stress test), and the last 10 minutes were for cooling (Coordination, balance, walking and breathing exercises). This exercise program was done with fast walking or endless jogging with the sloping floor to reach the desired intensity, as well as by bicycle, elliptical, and rowing. During the entire intervention, the patient was monitored by a *Polar Multisport RS800CX*, oximetry, and the Borg scale (0-10 points) to avoid exceeding the training intensity (60-80% or 80-90% MHR obtained by stress test, > 7 Borg scale). The inclination, resistance, or speed of the exercises was assigned according to the indicative parameters (MHR obtained by the stress test, VO_2, Borg) for moderate or high intensity.

STATISTIC ANALYSIS

A database was created in Microsoft Excel 16.0 with all patients and their results of tests and questionnaires pre and post-training. Then, descriptive statistics were carried out to estimate and display the data by means of their corresponding standard deviation. The normality of the data was assessed by the Kolmogorov-Smirnov test, and the indication of specificity was evident for all analyses. Also, the ANOVA analysis of variance (one-way analysis of variance) was used, and subsequently, post hoc tests through the Tukey test were used to assess the characteristics of the different age groups, genders, and anthropometry. In all

Table 3: Post workout changes. (N = 275).

	Experimental group		
Variable	Pre	Pos	p
Ejection fraction, (%)	40 ± 4.8	47 ± 5.6	0.001
Weight, (kg)	84 ± 10.7	75 ± 3.5	0.002
BMI	34 ± 3.1	28 ± 1.3	0.001
Abdominal circumference, (cm)	93 ± 7.5	88 ± 5.2	0.002
SBP	139 ± 11.3	129 ± 2.3	0.001
DBP	86 ± 6.2	80 ± 1.3	0.001
Fat, (%)	29 ± 4.4	21 ± 5.5	0.001
Muscle, (%)	32 ± 9.1	36 ± 5.7	0.001
Force (kg)	27 ± 9.3	38.2 ± 8.4	0.001
Sarcopenia, (%)	32.0	13.0	0.012
Calf circumference	37.9 ± 11.5	48.6 ± 4.2	0.000
Cholesterol (mg/dL)	195 ± 13.5	180 ± 11.4	0.001
Triglycerides (mg/dL)	130 ± 12.7	115 ± 11.3	0.000
LDL (mg/dL)	118 ± 23.4	102 ± 12.6	0.001
HDL (mg/dL)	41 ± 3.6	49 ± 4.4	0.001
Fasting glucose (mg/dL)	135 ± 11.3	123 ± 7.1	0.002
VO_2 Estimated	7.5 ± 5.7	13.9 ± 3.3	0.001
METs	2.1 ± 1.6	3.9 ± 0.9	0.003
Fatigue (FACT-F)	16.3 ± 9.7	5.5 ± 4.9	0.002
Quality of life	108 ± 14	121 ± 7.6	0.002
Distance traveled	243 ± 23	312 ± 29	0.001
MHR-stress test	156 ± 12	175 ± 14	0.001

BMI = body mass index. DBP = diastolic blood pressure. HDL = high-density lipoprotein. LDL = low intensity lipoprotein. METs = metabolic equivalent. mg/dL = milligrams over deciliters. MHR = maximum heart rate. SBP = systolic blood pressure. VO_2 = maximum oxygen consumption.

cases, a significance level of 5% ($p \leq 0.05$) was established, and everything done was carried out in the PRISMA program.

RESULTS

After initial exclusions (six patients did not want to participate) and withdrawals, 275 participants were included in the structured CRP using HIIT. Oncological diagnoses are described in *Table 1*. The baseline characteristics of the participants are described in *Table 2*. This study included 125 female participants (45.45%), median age was 56 ± 10. Most of the participants had more than 2 CVRFs, including overweight or/obesity (78%), abdominal obesity (88%), dyslipidemia (25%, hypertension (31%), diabetes mellitus (56%), renal disease (11%) and sedentary lifestyle (91%). Regarding the psychosocial status, half of the participants score for depression (57%) and anxiety (18%). The baseline estimated mean CRF in the participants confirmed their low functional status (METs 2.1 ± 1.6) with an estimated VO_2 (7.5 ± 5.7). Primary outcomes and exploratory outcomes are described below.

Primary outcome: effects on the CRF

There was a significant improvement in the functional capacity after the intervention reported in METs (2.1 ± 1.6 vs 3.9 ± 0.9, p = 0.003), currently to the improvement in the estimated VO_2 (7.5 ± 5.7 vs 13.9 ± 13.9 p = 0.001). Regarding the 6 MWT, improvements were noted (243 ± 23 vs 312 ± 29 mt, p = 0.001). It was found a significant improvement in LVEF (40 ± 4.8 vs 47 ± 5.6%, p = 0.001). Other significant improvements were noted in the SBP and DBP *(Table 2)*.

Primary outcome: effects on the QoL

It was reported a significant improvement in patient-perceived QoL (108 ± 14 vs 121 ± 7.6 p = 0.002) and improvements in the perceived participant fatigue (16.3 ± 9.7 vs 5.5 ± 4.9%, p = 0.002).

Exploratory outcomes: effects on anthropometrics parameters

There was a significant improvement in the participants' weight (84 ± 10.7 vs 75 ± 3.5 kg, p = 0.002), abdominal circumference (93 ± 7.5 vs 88 ± 5.2 cm, p = 0.002), fat percentage (29 ± 4.4 vs 21 ± 5.5%, p = 0.001), muscle percentage (32 ± 9.1 vs 36 ± 5.7%, p = 0.001), muscle strength (27 ± 9.3 vs 38.2 ± 8.4%, p = 0.001), and sarcopenia (32 vs 13%, p = 0.012) *(Table 3)*.

Exploratory outcomes: cardiovascular risk factors management

We noticed an improvement in the metabolic profile of the participants, including weight, lipid profile post-intervention, fasting glucose levels, SBP, and DBP, and as previously mentioned in the anthropometric effects of the intervention.

Safety and adverse events

After the different interventions in the research groups, we can mention that no adverse events, falls, or injuries were reported in the participants. The interventions were fully monitored, and no hemodynamic or metabolic alterations were identified in the research participants. Therefore, the interventions and protocols carried out demonstrated great safety in the study population.

DISCUSSION

The present study is one of the first to evaluate the effects of HIIT in oncological patients with a new diagnosis of CVD and low functional capacity. It compared the effects on CRF and QoL and other exploratory parameters such as CVRFs and anthropometric measurements. The main finding was the statistically significant improvement of the CRF (expressed as METs and estimated VO_2). An improvement of one MET has been demonstrated to reduce CV morbidity and mortality.[27] The effects of HIIT in oncological survivors have been investigated in other studies, and their results were related to an improvement up to 3.77

mL/kg/min ($p \leq 0.05$),[28] showing similar benefits to our study.

Recently, it has been possible to elucidate with a good level of evidence that the HIIT effect is capable not only of increasing the maximum thresholds of cardiorespiratory fitness (particularly of VO_2) but also of producing a greater degree of positive remodeling in patients with ventricular dysfunction, such as the case of cardio-oncology patients who usually have systolic or diastolic ventricular involvement.[29]

One of the main controversies concerning the intervention is the heterogeneity of the structure of HIIT. The variations of this aerobic resistance training modality respond not only to the number of intervals that the patient can sustain during a 30-minute session but also to the intensity and duration in which the high-intensity interval will be provided. Some studies have proposed HIITs from 30 seconds to 2 minutes, with active breaks of the same duration. This becomes relevant when the cut-off points for the maximum intensity of HIIT are established, which, in patients with heart disease, vary between 85 and 90% of VO_2peak or HR reserve, as it was performed in the first pilot studies with cardio-oncology rehabilitation (CORE).[30,31] What is certain is that, for the HIIT-based intervention to differ from MICT, it is important that not only do high-intensity intervals exist on a continuous moderate basis, but that, in general, the HIIT training volume should be hypercaloric compared to the one achieved in MICT, as has been attempted in training strategies in patients with chronic heart failure.[32] In our study, our high-intensity intervals were formulated in 30-second pulses at an intensity of almost 90% of the HRR, reaching for gains in cardiorespiratory fitness.

One of the great strengths of our study lies in the interdisciplinary intervention that patients received, beyond the HIIT strategy coupled with muscle strength training. The last one should be repeated until it becomes difficult to continue the exercise because of its effects on muscular function and body composition, as has been reported in the meta-analysis of Strasser B et al.[33] The control of risk factors and nutritional care with a view to metabolic control is part of the recognized processes within CORE, as established in the Scientific Statement from the American Heart Association.[34]

Health-related QoL is an important factor in this population due to the impact of the decreased functional dimensions of physical, social, cognitive, and emotional well-being. Previous and most recent evidence showed similar improvements of a HIIT intervention on global quality of life, physical functioning, role functioning, cognitive functioning, fatigue, pain, dyspnea, and insomnia compared to an inactive control group.[35] Cardio-oncology rehabilitation is a comprehensive approach with a focus on QoL, cardiovascular risk profile, and cardiorespiratory fitness, as developed in our study.[36]

Limitations

To further understand the impact of a structured CRP using HIIT, we need to compare the unique potential benefits of HIIT to a MICT control group, which in this study was not possible to do. We still have some questions about the impact and effects of a standard CRP in oncological survivors compared to only receiving standard care. We need to further evaluate the long-term effects of this intervention and to see if the potential benefits can be maintained during a prolonged time.

One of the remaining questions is to evaluate if the reported effects of the intervention can be greater by the underlying oncological diagnosis or to the specific presenting CVD.

A limitation to consider in this study is the absence of nutritional and pharmacological control and monitoring in this type of population. These are important interventions that contribute to the outcome of these patients. Therefore, it is suggested that for future research of this type, an analysis of these variables can be made and the participation of suitable professionals for this purpose, either in the role of co-authors or research advisors.

CONCLUSIONS

The overlap in risk factors and disease prevention for cancer and CVD suggests that both diseases share common underlying pathophysiology pathways, such as chronic inflammation, which would potentially lead to worse patient outcomes. For this reason, our study suggests that using HIIT intervention is an efficient way with a security profile to improve fitness capacity, QoL, and anthropometric parameters and control CVRF in participants survivors of cancer who presented a recent CV event or CVD. We further need more randomized control studies to establish clearer and stronger evidence of the effects of this type of training. These results need to be compared with moderate-intensity continuous training (MICT) to define a preference strategy in cardio-oncological patients.

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Data confidentiality: the authors declare that they have followed their workplace's protocols regarding the publication of patient data.

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