Efectos sobre la aparición de la toxicidad producida por el tratamiento oncológico mediante un programa de ejercicio terapéutico adaptado (ATOPE)

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Attenuating treatment-related toxicity in patients with cancer via a tailored therapeutic exercise program: ATOPE trial

Doctoral Thesis/ Tesis Doctoral

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A mis padres, a mi hermana, y a Sergio,

por haber estado siempre ahí, en la cercanía y la lejanía.

TABLA DE CONTENIDO

FINANCIACIÓN Y PROYECTOS DE INVESTICACIÓN

RESUMEN

La supervivencia al cáncer es un hecho en la mayoría de los casos, sobre todo ante tipos de cáncer en los que es posible una detección temprana, y subtipos de tumor menos agresivos. Esta supervivencia también se debe en parte al avance de la tecnología y del conocimiento, y con ello una disponibilidad de tratamientos más eficaces. Los tratamientos pueden ser locales o sistémicos, y aunque son necesarios y eficaces para la lucha contra la enfermedad, producen efectos adversos, no solo durante los mismos, sino que pueden aparecer muchos años después de que estos hayan finalizado. Además, este impacto que producen, puede aumentar la recidiva o la mortalidad de la persona, por lo que es crucial contar con herramientas que permitan un control del estado de salud de estos pacientes para detectar un declive de riesgo de forma precoz. Así, por ejemplo, la cardiotoxicidad es uno de los efectos adversos más importantes ya que puede provocar la aparición complicaciones cardíacas, relacionadas con 11% de las muertes tras el cáncer. Al efecto de los tratamientos se une además una serie de circunstancias y factores como: la edad avanzada, estilos de vida inadecuados, la presencia de comorbilidades o incluso el propio tumor. Esto ocasiona una amenaza múltiple, que sitúa a las personas con cáncer en un estado de salud frágil, que puede presentarse desde el mismo momento del diagnóstico. Esta situación no sólo los ha predispuesto a un mayor riesgo de sufrir cáncer, y a intensificar efectos adversos, sino que también los predispone a padecer otras enfermedades crónicas, entre las que destaca las cardiovasculares.

El ejercicio terapéutico ya se considera eficaz para el abordaje de la cardiotoxicidad. Sin embargo, estudios preclínicos parecen mostrar además su posible efecto preventivo. Esto nos lleva a pensar que el ejercicio terapéutico es un elemento fundamental en el tratamiento de las personas con cáncer; aunque debido al deteriorado estado de salud de estos pacientes, debe estar prescrito con dosis precisas y seguras, además de con un periodo de recuperación adecuado y personalizadas. La evidencia actual no es sólida sobre cuál es esta prescripción óptima. Por tanto, los objetivos del presente trabajo fueron: I) evaluar las secuelas del cáncer en el periodo de supervivencia, durante los tratamientos y al diagnóstico (sección 1) y II) diseñar y desarrollar un programa de ejercicio terapéutico para prevenir o mitigar la cardiotoxicidad; junto con herramientas para el apoyo de la prescripción de ejercicio. (sección 2). Para ello hemos presentado una herramienta para detectar alteraciones en la capacidad funcional, como reflejo de la salud física (estudio I), examinado las

alteraciones y estado de salud de pacientes al diagnóstico (estudio II), analizado los efectos del ejercicio terapéutico como prevención de la cardiotoxicidad, y diseñado y desarrollado un programa de ejercicio terapéutico enfocado a la prevención de la cardiotoxicidad (estudio IV), junto con una herramienta para apoyar la prescripción de una dosis de ejercicio físico y recuperación óptimas.

Los resultados de esta Tesis Doctoral aportan evidencia científica que apoyan el uso de herramientas para detectar las tendencias de recuperación o empeoramiento en pacientes con cáncer, la evaluación de alteraciones y el estado de salud al diagnóstico, y la utilización de ejercicio terapéutico para aumentar el conocimiento sobre la prevención de secuelas importantes como es la cardiotoxicidad, junto con una herramienta válida y fiable en pacientes con cáncer.

6

ABSTRACT

Cancer survival is guaranteed in most cases, especially in people in which the type of cancer diagnosed early screening is possible, and tumor subtypes are less aggressive. High survival rate is possible also partially due to the improvement of technology and knowledge of cancer biology, which result in the availability of more effective treatments. Treatments can be local or systemic, and although being necessary and effective to fight against the disease, they produce adverse effects, not only in patients during treatment itself, but can appear many years after their treatment has finished. Moreover, the impact of treatment can increase the recurrence or mortality of cancer in this population; so it is crucial to have tools to monitor health status of these patients for early risks detection. Thus, for example, cardiotoxicity is one of the most important adverse effects, as it can lead to the appearance of cardiac complications, which are related to 11% of deaths in people following cancer. Besides the side effects of cancer treatment, it is also important to consider a series of circumstances and factors such as advanced age, inadequate lifestyles, the presence of comorbidities or even the tumor itself. This is called a "multiple it" phenomenon, which places people with cancer in a fragile state of health, which may present from the very moment of diagnosis. This situation may predispose them not only to an elevated risk of cancer, and have worse side effects, but also to suffer from other chronic diseases, including cardiovascular disease.

Therapeutic exercise is already considered effective for cardiotoxicity management. However, preclinical studies also support a potential preventive effect. This leads us to think that therapeutic exercise is a key element in the management of people with cancer; although due to the deteriorated health state of these patients, a tailored, safe and precise prescription is needed, as well as an adequate recovery period. Current evidence is not solid on what this optimal prescription is. Therefore, the aims of the present work were: I) to evaluate sequelae of cancer in the patients during survival period, during treatments and at diagnosis (section 1) and II) to design and develop a therapeutic exercise program to prevent or mitigate cardiotoxicity; together with tools for the support of exercise prescription (section 2). To this end, we have presented a tool to detect alterations in functional capacity as a reflection of physical health (study I), examined the alterations and health status of patients at diagnosis (study II), analyze the effects of therapeutic exercise for the prevention of cardiotoxicity, and designed and developed a therapeutic exercise program focused on the prevention of cardiotoxicity (study IV),

together with a tool to support the prescription of an optimal physical exercise dose and recovery.

The results of this Doctoral Thesis provide scientific evidence to support the use of tools to detect recovery or worsening trends in cancer patients, the assessment of alterations and health status at diagnosis, and the use of therapeutic exercise to increase knowledge about the prevention of important sequelae such as cardiotoxicity, together with a valid and reliable tool in cancer patients.

ABREVIATURAS

ATOPE+: sistema móvil de salud ATOPE+

ATOPE: programa de ejercicio terapéutico personalizado

INTRODUCCIÓN

GENERAL

GENERAL INTRODUCTION

INTRODUCCIÓN GENERAL

Situación actual del cáncer

La palabra *cáncer* engloba a un grupo de enfermedades muy amplio, capaces de afectar a cualquier parte de nuestro organismo. De forma global, es una de las principales causas de muerte en la población, siendo en el año 2020 responsable de alrededor de 10 millones de fallecimientos[1]. Sin embargo, la incidencia del cáncer es con creces más alta que la mortalidad. Según el *Global Cancer Observatory, de* la Agencia Internacional para la Investigación del Cáncer y la Organización Mundial de la Salud, en el año 2020 nos situamos con un total de casi 19,3 millones de casos nuevos en el mundo, con la expectativa de que en 2040 la incidencia sea de 30,2 millones de casos[1]. En el año 2020, en España, la incidencia se situó en 282 mil casos anuales[1], y según las estadísticas del Registro de Cáncer de Granada[2], en 2020 a nivel de Andalucía los casos nuevos de cáncer fueron más de 43 mil. Asimismo, y citando los datos que se han recogido por provincias, la incidencia de cáncer es superior a la media de Andalucía en Huelva, Sevilla y Cádiz en ambos sexos, mientras que a la cola se situaron Málaga (en hombres), Córdoba (en mujeres) y Jaén y Granada (hombres y mujeres)[2]. En concreto, para la provincia de Granada, la incidencia ha ido aumentando entre los

años 1985 y 2017 de forma progresiva, con un porcentaje de cambio anual del 2,2% en mujeres, y de 1,4% en los hombres, para todo tipo de cáncer incluyendo el cáncer de piel no melanoma[2].

A nivel mundial, en ambos sexos, los tipos de cáncer más frecuentes son el de mama, próstata, pulmón y colorrecto[1]. En España, el tipo de cáncer más común en mujeres es el de mama, seguido por el de colorrectal, pulmón y cuerpo uterino; entre hombres, el de próstata, seguido por el de pulmón, colorrectal y vejiga; y teniendo en cuenta ambos sexos el de colorrecto[1]. Ocurre de forma similar en Andalucía, en la que según las estadísticas del Registro de Cáncer de Granada[2], sin tener en cuenta el cáncer de piel y de forma similar a España, los tipos de cáncer más frecuentes son en mujeres de mama, colorrectal y cuerpo uterino; y en hombres, de próstata, pulmón y vejiga urinaria.

La etiología de esta enfermedad es de tipo multifactorial, ya que hay distintos factores de riesgo no modificables y modificables relacionados con la aparición del cáncer. Por un lado, como factores no modificables nos encontramos factores genéticos, historial familiar de cáncer, el sexo, la raza y edad - la incidencia del cáncer es mucho más alta en personas con edad avanzada[3], donde la capacidad del organismo para

responder a agresiones es más deficitaria[4]; otros que pueden ser modificables o no modificables como la exposición a la radiación ultravioleta, la ionizante, o a la contaminación[1]; y hay muchos factores modificables relacionados con estilos de vida y comportamientos respecto a la salud, como por ejemplo, el uso del alcohol y de tabaco, una dieta inadecuada, la inactividad física, el sobrepeso o la obesidad[5]. Éstos, han ganado peso en los últimos años, y de hecho, se estima que hay un porcentaje de hasta el 50% de casos de cáncer que podrían ser evitables a través de la modificación de estilos de vida[6,7].

Supervivencia del cáncer

La supervivencia del cáncer ha aumentado en las últimas décadas: tipos de cáncer como el de mama o colorrectal sólo llegaban al 40%[8] y 23%[9] respectivamente, de personas que sobreviven la enfermedad en un periodo de 5 años; mientras que actualmente pueden ascender al 90% y 67% respectivamente[10]. Las cifras de supervivencia en pacientes de cáncer fluctúan dependiendo tipo de cáncer que se diagnostica, el estadio en el que se diagnostica y el tratamiento disponible[11]. Para tipos de cáncer como el de mama y el colorrectal, la supervivencia depende de su detección y tratamiento tempranas[11], y puede haber muchas diferencias a nivel mundial para los países que tienen un elevado Índice de Desarrollo Humano[10]. Por el contrario, para tipos de cáncer como el de pulmón o páncreas, en el que no hay un cribado y un tratamiento tan efectivos[11], los ratios de supervivencia no varían tanto entre países[10].

Para países como Canadá o Estados unidos, la supervivencia de los tipos de cáncer más frecuentes, se sitúan en un 88-90% para el cáncer de mama, en un 94-97% para el de próstata, en un 65-67% para el de colorrecto, mientras que de pulmón se sitúa en un 21%. En Europa, la supervivencia varía para el cáncer de mama desde un 77% a un 86%, el de próstata de un 78% a un 94%, el colorrectal de un 48% a un 68%, mientras que el de pulmón es de un 11% a un 20%[10]. En España, los datos se sitúan favorablemente arriba respecto a los datos europeos, excepto en el cáncer de pulmón que se sitúa a la baja respecto a Europa[10]. Las cifras de supervivencia en Granada se encuentran también en el extremo más alto del rango europeo; siendo las tasas de supervivencia del 88% en cáncer de mama, de un 85,6% en cáncer de próstata, entre un 55-60% en colorrectal, e igualmente que en los rangos españoles, la supervivencia fue de las más bajas en cáncer de pulmón dentro del rango europeo (16,4% en mujeres pero del 8,1% en hombres)[12].

Este aumento de la supervivencia se ha debido principalmente a los avances en la

detección precoz y en el tratamiento médico del cáncer[13]. Esto ha causado que las cifras de mortalidad en el año 2020 a nivel mundial fuesen a aproximadamente de menos de 10 millones de casos[1]. En España, las cifras de mortalidad en 2020 fueron de 113 mil casos[1]. En la provincia de Granada, los datos de mortalidad fueron del periodo de 2012-2014, y supusieron una media de 1.859 defunciones anuales[14].

Tratamiento oncológico

Las combinaciones dentro del tratamiento para el cáncer pueden ser muy variadas y se puede apreciar en que la National Comprehensive Cancer Network establece unas guías de tratamiento para el cáncer por localización, que pueden llegar a cientos de páginas cada una, donde se detallan también las pautas de los tratamientos a seguir según las características específicas de ese tipo de cáncer, junto con la situación individual de cada paciente[15]. Hay muchos tipos de tratamiento como la cirugía, la radioterapia, la quimioterapia, la inmunoterapia, la terapia dirigida y la hormonoterapia[16].

En las últimas décadas, los tratamientos han experimentado un gran avance, y siguen siendo objeto de estudio para mejorar su seguridad y eficacia[16–18]. Por ejemplo, la cirugía que juega un papel principal como modalidad para la mayoría de tipos de cáncer[19]. En lo que respecta a ésta, en las últimas décadas se ha producido un cambio de paradigma. Sin llegar a comprometer la supervivencia, se ha intentado evitar los efectos de la cirugía radical, conservando la forma, función y calidad de vida de los pacientes; gracias al avance de la tecnología y el uso de terapias multimodales, como la radioterapia, la quimioterapia y la terapia hormonal, en combinación con una cirugía mínimamente invasiva[19]. Otro ejemplo es la quimioterapia, donde se han desarrollado una gran variedad de compuestos que actúan de diferente forma ante el proceso cancerígeno, debido a la mejor comprensión molecular del cáncer, y debido a la resistencia que se desarrolla ante algunos tipos de quimioterapia[18].

Sin embargo, los tratamientos pueden llegar a causar una amplia gama de toxicidades y tener un alto impacto en estos pacientes por las secuelas que implican[20–23].

Secuelas más frecuentes

Los efectos secundarios se pueden clasifican en agudos (aquellos que ocurren antes o durante los tratamientos), crónicos (aquellos que persisten por meses o años durante los tratamientos) o tardíos (aquellos que pueden desarrollarse meses o años después del tratamiento[24]. Entre los efectos adversos agudos se encuentran las náuseas, vómitos, erupciones cutáneas, neuropatías periféricas, pérdida de cabello, disminución de la función física, fatiga,

dolor, ansiedad, depresión, cambios en la autoestima e imagen corporal, y una disminución de la función emocional.

Entre los efectos crónicos/tardíos, cabe destacar la fatiga que se presenta en 80-100% de los pacientes[23], y es común a todos los tratamientos que estos pacientes reciben[25]; y las complicaciones cardiovasculares, ya que son las que tienen más impacto en el desarrollo de comorbilidades[26] o de la mortalidad[27–29], y presentan una prevalencia de hasta del 50%[23]. La prevalencia de otras secuelas importantes son: dolor en alrededor de un 59%, deterioro cognitivo en hasta un 75%, neurotoxicidad en hasta un 68%, trastornos del sueño en hasta un 70%, toxicidad metabólica en hasta un 87% y distrés psicológico en hasta un 27% de los pacientes, y daño en el tejido óseo de 2-10 veces más rápido que en individuos sanos[23]. Cabe mencionar que las secuelas producidas por los tratamientos son más amplias que las aquí recogidas, y algunas sólo específicas de un tipo de cáncer[30].

Es importante señalar el gran impacto que todas estas secuelas tienen en la calidad de vida o en la salud general[31,32], siendo especialmente importante el impacto que provoca en la salud física[33]. La fatiga[34], el dolor[34,35], la pérdida de masa muscular[36], la depresión[37], y falta de tiempo o la kinesiophobia[38], además de otros efectos

adversos de los tratamientos, reducen la capacidad y la motivación de realizar actividad física[39,40], ocasionando que muchos supervivientes de cáncer reduzcan su movimiento a lo largo del día[39,41]. Esta inmovilidad, puede reducir la capacidad funcional, y producir alteraciones a nivel del muscular[42] y cardiovascular[43]. Pero además, es importante considerar, que la capacidad funcional ha sido mostrada como un indicador del pronóstico y la supervivencia en personas con cáncer[44].

Por tanto, es fundamental contar con herramientas óptimas, accesibles y de fácil uso, que faciliten la valoración del estado de salud físico y también la monitorización de la mejora y el deterioro de estos pacientes.

Perfil del superviviente de cáncer

Además del impacto de los tratamientos, hay otros factores que refuerzan la aparición o gravedad de estos efectos secundarios, como se plantea en la teoría del "*multiple hit*" de Jones et al.[45]. Por ejemplo, factores como el estado de salud de estos pacientes, es decir, la presencia de enfermedades o situaciones preexistentes (como algunos relacionados con estilos de vida como la inactividad física, sobrepeso, etc.)) pueden llegar a alterar el equilibrio fisiológico[46]. A esto se une los efectos de la propia enfermedad: a parte de los efectos locales del tumor, los pacientes presentan un perfil inflamatorio crónico que es el

resultado de la compleja combinación de factores secretados por el tumor y la respuesta inmune/inflamatoria desequilibrada del huésped ante la presencia del tumor[47]. En conjunto, hacen que el paciente sea más propenso no solo a sufrir los efectos secundarios de los tratamientos, sino que estos puedan ser más graves[48] y exista un aumento de riesgo de comorbilidades, como alteraciones cardiovasculares, y de mortalidad[49] por ejemplo por causas cardiovasculares[45].

Siguiendo este modelo[45], es evidente, que las personas con cáncer pueden presentar una posible situación de vulnerabilidad[50]. Por tanto, ya en el momento del diagnóstico, estos factores a falta de haber recibido tratamiento médico-quirúrgico, podrían favorecer un estado fisiológico alterado o cierta fragilidad fisiológica, que se vería posteriormente reforzada.

Estudios previos ya han mostrado alteraciones descritas desde el diagnóstico, entre otras: fatiga[51], presencia de factores de riesgo para enfermedades cardiovasculares[52], caquexia[53,54], ansiedad y depresión[55], y niveles altos de distrés[56,57].

La identificación de las secuelas y estado de salud, y valoración de posibles alteraciones en el momento del diagnóstico, podría ayudar a diseñar intervenciones eficaces con el fin de prevenir el impacto posterior en la salud y calidad de vida.

Alteraciones cardiovasculares y cáncer

La tasa de mortalidad en esta población por enfermedades cardiovasculares es preocupante: en una cohorte de más de 7 millones de pacientes con cáncer, la mortalidad por enfermedades cardíacas fue de más de un 10% por 10.000 personas-año; y el riesgo de muerte que presentan por estas causas es de 2,24 veces mayor que la población sana [58].

Las enfermedades cardiovasculares están estrechamente ligadas al cáncer. Muchas de las personas que tienen cáncer, tienen alguna enfermedad cardíaca y viceversa. Esto puede ser debido a que comparten algunos mecanismos biológicos[59] que contribuyen al aumento de ambas incidencias[60]. El cáncer y las enfermedades cardiovasculares comparten factores de riesgo[61]: la edad avanzada, otras comorbilidades de tipo cardiovascular[62], y estilos de vida poco adecuados, como la obesidad, y la inactividad física[62,63] que favorecen su aparición. Debido a su prevalencia, dan lugar a una población en la que estas dos condiciones pueden estar presentes a la vez. Pero además, muchos de los tratamientos (e.g. quimioterapia, radioterapia, inmunoterapia, etc.), tienen un efecto toxico a nivel cardiovascular[64], que puede aparecer tanto de forma aguda como crónica[65], y aumenta el riego de

desarrollar enfermedades cardiovasculares[66].

La cardiotoxicidad se define como una reducción de un 5% de la fracción de eyección del ventrículo izquierdo (cardiotoxicidad subclínica)[67], o como valores por debajo del 50% de la fracción de eyección del ventrículo izquierdo[68]; y puede ser transitoria o permanente[69]. Es importante destacar que además de incrementar el riesgo de morbilidad y mortalidad[70], puede llegar a ser causa de la interrupción del tratamiento médico[71], lo que reduciría la eficacia del mismo y la supervivencia en estos pacientes.

Debido al importante rol en la salud y supervivencia al cáncer que las enfermedades cardiovasculares tienen en la población oncológica, es esencial el planteamiento de intervenciones preventivas con un enfoque cardioprotector[72].

Fisioterapia para el abordaje de la cardiotoxicidad

El ejercicio terapéutico ya es reconocido por su efecto cardioprotector en la población general y en pacientes con enfermedades cardíacas[73]. Además, puede ser un instrumento esencial en el tratamiento de la cardiotoxicidad en pacientes con cáncer[74,75]. Sin embargo, la evidencia respecto a su papel preventivo ha sido más estudiada en

estudios preclínicos y la dosis óptimas para pacientes aún no se ha esclarecido[76], ya que no hay suficientes resultados mostrando beneficios del ejercicio físico en la función cardiovascular en esta población. Sin embargo esto no significa que estos pacientes deban ser inactivos o sedentarios[20].

Por la situación de vulnerabilidad de las personas con cáncer, la prescripción de ejercicio físico debe realizarse con dosis individualizada, de acuerdo a los parámetros de frecuencia, la intensidad, la duración, y el tipo de ejercicio físico[77], y progresando de acuerdo a su estado de salud y sintomatología. En este contexto, una prescripción no lineal podría maximizar la adaptación al ejercicio físico, permitiendo tiempos de recuperación adecuados, y haciendo prescripciones de ejercicio seguras[60]. En los pacientes con cáncer, monitorizar el estado de recuperación es de suma importancia, ya que se encuentran en una situación de vulnerabilidad por el cáncer y sus tratamientos, con alteraciones similares[78–80] a las que suceden con el sobreentrenamiento en deportistas[81]. De no ser monitorizadas, estas alteraciones de forma continuada, podrían llevar a una disminución de la capacidad de asimilación del ejercicio o incluso al *overreaching*[82]; o alteraciones graves como más predisposición a enfermar y aumento del riesgo de mortalidad[83].

18

Para evitar esta situación, se ha utilizado la variabilidad de la frecuencia cardíaca para guiar la prescripción, ya que podría permitir un mejor ajuste de la dosis, y evitar el sobreentrenamiento[84]. Esta modalidad ha sido ampliamente estudiada en deportistas[85], pero su uso no es está muy extendido a otras poblaciones clínicas, ni en pacientes con cáncer. Además, la puesta en marcha de estudios que utilicen este tipo de prescripción es complejo, pero el uso de nuevas tecnologías puede ofrecer una optimización de este recurso[86]. De hecho, hay algunas aplicaciones desarrolladas y utilizadas en el mundo del rendimiento[87–89]. Sin embargo, no existe hasta donde sabemos ninguna en otras poblaciones clínicas o en cáncer.

Por tanto, es muy importante que se desarrollen herramientas específicas para cáncer y que sean validadas ya que se dirigen a una población compleja. Esto permitiría dar un paso hacia una monitorización rápida del estado de recuperación en estos pacientes, con una evaluación completa a distancia, para apoyar la prescripción de dosis de ejercicio físico, respetando los periodos de carga y recuperación de cada paciente, y de forma individualizada.

Por tanto, nos encontramos en una situación en la que los pacientes con cáncer pueden llegar a tener un amplio abanico de secuelas que pueden llegar a tener un alto impacto en ellos; por lo que herramientas de fácil uso, para el seguimiento de la mejora y el deterioro de estos pacientes son fundamentales. Por otro lado, que los pacientes pueden tener alteraciones a veces desde el diagnóstico, por lo que es necesario valoraciones tempranas tanto de las secuelas, como del estado de salud. Seguidamente que una de las secuelas más importantes es la cardiotoxicidad, pero que, aunque el ejercicio físico se ha utilizado como tratamiento, la evidencia es insuficiente en cuanto a sus efectos preventivos; ni qué dosis individualizada se necesita para mitigarlo. Las nuevas tecnologías podrían ser una forma factible y sencilla de ofrecer una herramienta que permite dar un paso hacia adelante en el apoyo para la prescripción de ejercicio. Sin embargo, es necesario que en poblaciones como la oncológica, estas herramientas sean accesibles, intuitivas y estén validadas, ya que es una población vulnerable.

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26

OBJETIVOS

AIMS

OBJETIVOS

Los objetivos principales o generales de esta Tesis Doctoral son los siguientes: analizar las secuelas del cáncer en el periodo de supervivencia, durante los tratamientos y al diagnóstico (Sección 1); y diseñar y desarrollar un programa de ejercicio terapéutico para prevenir o mitigar la cardiotoxicidad; junto con herramientas para el apoyo de la prescripción de ejercicio. (Sección 2).

Para ello, se proponen los siguientes objetivos específicos organizados por secciones:

Sección 1: Evaluación de las secuelas del cáncer en el periodo de supervivencia, durante los tratamientos y al diagnóstico.

1. Estudio I: Determinar una herramienta que permita determinar alteraciones en la capacidad funcional, como reflejo de la salud física, en pacientes supervivientes y durante los tratamientos.

2. Estudio II. Examinar las alteraciones y el estado de salud de los pacientes con cáncer en el momento del diagnóstico.

Sección 2: Ejercicio terapéutico como herramienta para la prevención de la cardiotoxicidad.

3. Estudio III: Analizar los efectos y la dosis óptima de ejercicio terapéutico para prevenir o mitigar la cardiotoxicidad de los tratamientos oncológicos.

4. Estudio IV: Diseñar y desarrollar un programa de ejercicio terapéutico personalizado () para prevenir o mitigar la toxicidad a nivel cardíaco antes y durante los tratamientos

5. Estudio V: validar un sistema móvil de salud (ATOPE+) para monitorización remota del balance del sistema nervioso autónomo, percepción de recuperación, satisfacción del sueño, distrés emocional y fatiga.

AIMS

The main or general aims of this Doctoral Thesis are the following: to analyze the sequelae of cancer in the survival period, during treatments and at diagnosis (Section 1); and to design and develop a therapeutic exercise program to prevent or mitigate cardiotoxicity; together with tools for the support of exercise prescription (section 2).

To this end, the following specific objectives are proposed, organized by sections:

Section 1: Evaluation of cancer sequelae in the survival period, during treatments and at diagnosis.

1. Study I: To determine a tool to assess alterations in functional capacity, as a reflection of physical health, in cancer patients during and after treatments.
2. Study II. To examine alterations and health status at diagnosis of patients with cancer.

Section 2: Therapeutic exercise as a tool for the prevention of toxicity.

3. Study III: To analyze the effects of therapeutic exercise to prevent or mitigate cardiotoxicity; and to determine an optimal dose for the same purpose in patients with cancer.
4. Study IV: Design and develop a tailored therapeutic exercise program (ATOPE) to prevent or mitigate cardiotoxicity before and during treatments.
5. Study V: Validate a mobile health system (ATOPE+) for remote monitoring of autonomic nervous system balance, perception of recovery, sleep satisfaction, emotional distress and fatigue.

MATERIAL Y MÉTODOS, RESULTADOS, DISCUSIÓN

METHODS
RESULTS
DISCUSSION

Table 1. Characteristics of the articles included in the present International Doctoral Thesis.

Article	Design	Participants	Outcomes
Section 1: Determine reference values to support de assessment of decline of physical function in survivors and the evaluation of the baseline side effects and health status of cancer patients upon diagnosis			
I. The minimal clinically important difference in the treadmill six-minute walk test in active women with breast cancer during and after oncological treatments	Cross-sectional study	Women with breast cancer during (n=38) and after treatment (n=74).	-Quality of life (EORTCL-QLQ C30 physical function domain). -Treadmill 6-minute walk test distance
II. Colorectal cancer pain upon diagnosis and after treatment: a cross-sectional comparison with healthy matched controls	Cross-sectional study	Colorectal cancer patients. Newly diagnosed (n=29), post treatment (n=40), and healthy matched controls (n=40).	-Pressure pain threshold (algometer), self-report spontaneous pain (VAS). -Abdominal isometric strength (trunk curl test). -Muscle structure (ultrasound) -Anthropometry and body composition (impedanciometer, waist circumference).
Section 2: Therapeutic exercise to prevent or mitigate medical treatment toxicity.			

III. Cardiotoxicity and therapeutic exercise in breast cancer: effects and dose. Systematic review and meta-analysis	Systematic review and meta-analysis	Women with breast cancer (n=947).	-Cardiac function (echocardiography) -Biomarkers -Hemodynamics -Exercise capacity (6MWT distance, VO2max)
IV. Attenuating treatment-related cardiotoxicity in women recently diagnosed with breast cancer via a tailored therapeutic exercise program: protocol of the ATOPE trial	Protocol study ClinicalTrials.gov, NCT03787966	Women recently diagnosed with breast cancer (before cancer treatment, n=29; during cancer treatment, n=29).	Feasibility -Recruitment rate -Perceived health status change -Adherence -Retention -Safety and adverse effects -Barriers and facilitators Efficacy -Cardiotoxicity (echocardiography) -Cardiovascular events -Cardiac autonomic function (electrocardiogram) -Quality of life (EORTCL-QLQC30 and BR23) -Cancer treatment sessions -ATOPE sessions

			-Overall survival
			-Comorbidities (Charlson Comorbidity Index)
			-Cardiorespiratory fitness (maximal exercise test)
			-Strength (dynamometer)
			-Flexibility (sit-and-reach rest)
			-Anthropometric and body composition (waist and hip circumferences, Inbody)
			-Muscle quantity (echography)
			-Oxidative stress, immune status, systemic inflammation.
V. mHealth system (ATOPE+) to support exercise prescription in breast cancer survivors: A validity and reliability, cross-sectional observational study (ATOPE study)	Validity and reliability cross-sectional study	Breast cancer survivors (n=22)	-Autonomic nervous system balance (electrocardiography and electrocardiograph-chest band)
			-Perception of recovery (perception of recovery scale and ATOPE+ scale)
			-Sleep satisfaction (Sleep diary subscale and ATOPE+ scale)
			-Emotional distress (Emotional distress thermometer of the National Comprehensive Cancer Network and ATOPE+ scale).

-Fatigue (sit-to-stand test and the rating of perceived exertion BORG scale, and ATOPE+ scale)

STUDY I

THE MINIMAL CLINICALLY IMPORTANT DIFFERENCE IN THE TREADMILL SIX-MINUTE WALK TEST IN ACTIVE WOMEN WITH BREAST CANCER DURING AND AFTER ONCOLOGICAL TREATMENTS

Disability and Rehabilitation

2022

STUDY I. THE MINIMAL CLINICALLY IMPORTANT DIFFERENCE IN THE TREADMILL SIX-MINUTE WALK TEST IN ACTIVE WOMEN WITH BREAST CANCER DURING AND AFTER ONCOLOGICAL TREATMENTS

ABSTRACT

Purpose: To examine the minimal clinically important difference (MCID) in the treadmill 6-minute walk test (6MWT) in women with breast cancer.

Materials and methods: A secondary analysis of cross-sectional data from 112 women who were undergoing chemotherapy or had undergone anticancer treatment was conducted. Participants completed the 6MWT on a treadmill and the European Organization for Research and Treatment of Cancer Questionnaire (EORTC-QLQ-C30) twice, eight weeks apart. Change in the physical function domain of the EORTC-QLQ-C30 was used to classify the 'positive change' subgroup (≥5 points difference) and the 'unchanged' subgroup (<5 points difference). This was combined with the distance difference from the 6MWTs, determining the MCID as the cut-off from the area under the receiver operating characteristic (AUROC) curve (anchor-based determination). The MCID was also determined from 1) the effect size and 2) the difference in standard error (SEM) of the results of the first and second 6MWT (distribution-based determination).

Results: The MCIDs in the during-chemotherapy group was 66.5 and 41.5 m respectively and those in the after-treatment group to be 41.4 and 40.5 m (SEM and effect size-based based respectively)

Conclusions: The MCID in the treadmill 6MWT distance could be used to interpret changes in the physical health status of women with breast cancer.

INTRODUCTION

Breast cancer and its treatment have important impacts on women's health, including physical and psychological alterations [1] and even loss of functional capacity [2]. Functional capacity is the ability to perform activities of daily living. Particularly important among them is the ability to walk since it facilitates self-sufficiency and provides information about the state of the cardiopulmonary [3] and musculoskeletal systems[4]. The 6-minute walk test (6MWT) – a submaximal walking test – is commonly used to determine functional exercise capacity in patients with different ailments, including cancer [5]. Indeed, it is often used in rehabilitation in oncology patients since it is easily performed [5] and provides prognostic and survival information [6], and key information is provided by the minimal clinically important difference (MCID) in the walked distance.

The MCID is the smallest change required to affect patient-perceived outcomes and, hence, reflects whether the change is relevant [7]. The MCID is valuable to patients with cancer, clinicians and researchers, and allows interpretation of any change in performance of the 6MWT. Identification of reference values that highlight changes in patients' health with cancer is essential to analyse trends in

recovery and to provide adequate interventions. This will help to offer a continuum cancer care to prevent physical deterioration [8]. Anchor- and distribution-based methods are the most commonly used methods to calculate the MCID [9], and the combination of these approaches has been previously used successfully to determine the MCID in the 6MWT [9].

A review [10] established that the MCID of the 6MWT for the geriatric population is between 14 and 30.5 metres, and 44 metres has been considered meaningful progress in people after stroke [11]. Considering certain cancer settings, Granger and collaborators [12] obtained the MCID in adults with lung cancer and identified an MCID ranging from 22 to 42 metres. Meanwhile, Shan and collaborators [13] worked with patients with multiple myeloma undergoing autologous haematopoietic cell transplantation (auto-HCT), although their efforts were inconclusive due to the lack of practicality of the 6MWT. To our knowledge, the MCID of the 6MWT in breast cancer is not known in either active cancer patients or cancer survivors, that meet the minimum recommendations of 150-300 minutes of moderate, or the equivalent of 75-150 minutes of vigorous physical activity [14]. Knowledge of the MCID for this group of patients would further support rehabilitation professionals involved in the oncology setting.

The consensus [15] on the performance of the 6MWT advises the use of a 30-m hallway without obstacles or distractions for standardization and optimal conduction of the 6MWT. However, many rehabilitation facilities have insufficient space to meet these requirements, which has led clinicians and researchers to investigate the use of alternative distances and even treadmills [16] as possible substitutes to the recommended hallway [15]. Despite helping to improve the feasibility of conducting the 6MWT in areas with limited space, the use of a treadmill for the 6MWT remains controversial. While some studies have shown that a treadmill is an adequate alternative to assess the distance walked (the primary endpoint of the test) [17] and the heart rate achieved during the 6MWT [18], other studies have found significant differences in the distance walked when the 6MWT is performed on a treadmill rather than overground [18–20]. In general, it appears that distances walked in the 6MWT on a treadmill are shorter than the distances achieved using the overground gold standard approach [19,20]. Several hypothesized reasons for this difference include lack of familiarization with the treadmill [19,21], a constant and limited speed [21], and different walking biomechanics compared to overground walking [22]. Based on the currently available evidence, normal reference data for the 6MWT completed on the ground versus the treadmill are not interchangeable.

Despite this, studies have used the treadmill for performing the 6MWT to check the health status of patients with chronic obstructive pulmonary disease [23] or pulmonary arterial hypertension[24], with few conducted specifically in cancer and even less in patients with breast cancer [25,26]. More studies are needed to standardize the development of the 6MWT on treadmills[16]. Therefore, this study aims to determine the MCID of the treadmill 6MWT in a sample of active patients with breast cancer, in two different situations: during anticancer treatment (during-chemotherapy group) and once these treatments have been completed (after-treatment group).

METHODS

Study design and sample

A secondary analysis was carried out with two data sets from two randomized controlled trials developed by the CUIDATE group (from the PAIDI BIO277 group): e-CUIDATECHEMO (Clinicaltrials.gov NCT02350582) [27] and eCUIDATE (Clinicaltrials.gov NCT01801527)[25], which were approved by the Research Ethics Committee of the University of Granada (FIS PI10/02749-02764 and PI-0457-2010, respectively) (Figure 1). In these studies, the

Figure 1: Patients flow in both studies
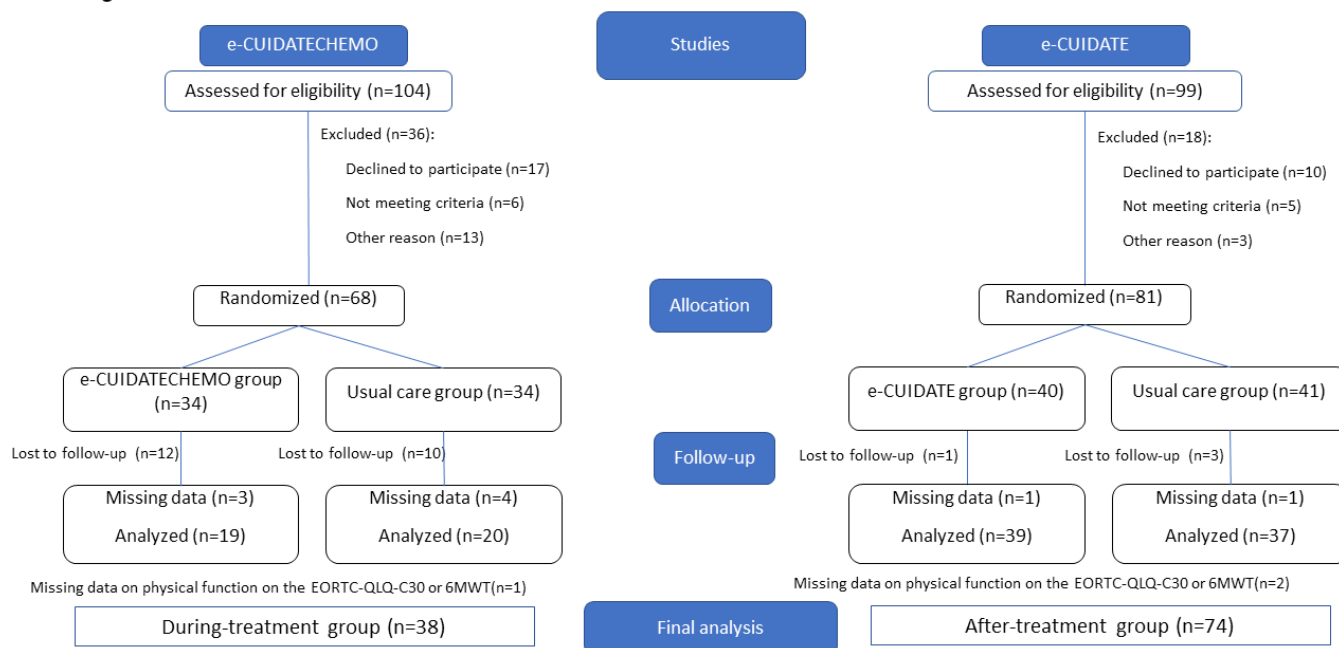
participants enrolled in a physical exercise program in accordance with the American College of Sport Medicine recommendations for patients with cancer [8]; the intervention group participated in 3 sessions per week during 8 weeks, and the control group received written recommendations. The STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement was followed [28]. Participants were referred by their treating oncologist at the Virgen de las Nieves Hospital (Oncology and Breast Unit) from March 2012 to November 2013 (eCUIDATE) and from September 2013 to June 2015 (e-CUIDATECHEMO).

Participants included had previously participated in the study e-CUIDATECHEMO and eCUIDATE study. The sample consisted

of women of women between 25 and 80 years old, with breast cancer diagnosis (I-IIIa), either undergoing chemotherapy (e-CUIDATECHEMO) or had finished oncological treatment (eCUIDATE), with no medical contraindications to perform physical exercise, that followed 8 weeks of physical exercise in accordance with the American College of Sport Medicine recommendations for patients with cancer. Patients were excluded of these studies if they had a chronic disease or orthopaedic issues that influenced their physical abilities. Also, for the current analysis, participants were excluded if they missed data on physical function on the EORTC-QLQ-C30 or the distance in the treadmill 6MWT (Figure 1)

Procedure and outcome measures

44

Participants recruited to both RCTs performed the 6MWT and completed the European Organization for Research and Treatment of Cancer questionnaire (EORTC-QLQ-C30) at baseline and again 8 weeks later. All assessments were completed in the physiotherapy laboratory in the Health Science Faculty from Granada by the same blinded physiotherapist from the CUIDATE group, who had 4 years of experience in the evaluation of patients with cancer, according to the Helsinki Declaration (WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 2017) and the Spanish Biomedical Research Law (Organic Law 14/2007, of 3rd July).

The 6MWT assessments were performed according to the European Respiratory Society/American Thoracic Society instructions [29], with the exception of being conducted on a treadmill instead of overground. The treadmill (H-P-COSMOS for graphics, Germany) test was performed using a previously published protocol [30] (Supplementary material 1). All participants received familiarization training on the treadmill and were asked to rest, sitting for more than 10 minutes, prior to testing. The Borg rating of Perceived Exertion (RPE), peripheral capillary oxygen saturation (SpO2) and heart rate were collected before and after the test as control variables. Participants were instructed to walk as fast as possible for 6 minutes with no treadmill inclination and an initial speed of 0. Participants were able to see only the speed, which they were able to increase or decrease by themselves. The test was performed twice by each participant with an active rest period of 15 minutes. The greatest 6MWT distance in metres was included in the analysis. This test has shown good reliability, with an intraclass correlation coefficient (ICC) of 0.78 for distance[30].

The physical function (PF) domain of the EORTC-QLQ-C30 Spanish version 3.0 was used as an anchor to calculate the MCID. This questionnaire includes both single- and multi-item scales (functional, symptoms and six single items) that are rated from 1 (not at all) to 4 (very much) and are transformed into a score of 0 to 100. A change > 5 points in PF is considered a minimal relevant threshold [31] and was used to classify participants into subgroups that achieved a 'positive change' (≥5 points) or remained 'unchanged' (<5 points) between time points [32]. The PF domain has a test-retest reliability of r=0.91 [33].

The demographic and clinical characteristics of participants were collected with a self-report questionnaire, a plastic tape measure and bioelectrical impedance analysis (InBody 720; Biospace, Gateshead, UK).

Statistical analysis

Analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistic for Windows, Armonk, NY, USA version 24.0). Only participants with repeated 6MWT and PF domain results were considered for analysis. The normality of the distribution of the variables was checked with the Shapiro-Wilk test. The demographic and clinical characteristics are expressed as the mean (m) and standard deviation (SD) for continuous variables and as a number (n) and percentage (%) for categorical variables. Based on the PF domain results, participants were divided into a 'positive change' subgroup (≥5 points difference in the PF domain between baseline and follow-up) and an 'unchanged' subgroup (<5 points difference in the PF domain between baseline and follow-up) [12]. The differences between groups in demographic and clinical characteristics were calculated using t tests for independent samples (continuous variables) and X^2 analysis (categorical variables). The change in 6MWT distance and PF domain between two time points was calculated using repeated-measures ANOVA. The test-retest reliability was calculated with an intraclass correlation coefficient (ICC).

The anchor-based method contrasts the change in a patient-reported outcome with another measure of change [34]. To determine whether the change in the 6MWT established a difference between the 'positive change' and 'unchanged' subgroups (with the PF domain of EORTC-QLQ-C30 as the anchor), we calculated the sensitivity and specificity for each cut-off point. The optimal cut-off point was obtained with the Youden Index [35]. Distribution-based methods were used to determine the MCID based on statistical

characteristics of the patient-reported outcomes with different methods, such as the standard error of measurement (SEM) and effect size (ES) [34], using the following formulas: SEM=$\sigma_1 \sqrt{(1-r)}$, where σ_1= standard deviation (SD) at baseline r= test-retest reliability coefficient and ES=0.5 X SD of the change in distance in the 6MWT [12].

RESULTS

Demographic and clinical characteristics

One hundred and twelve patients with breast cancer were included in this study. The average age of the participants were mean (SD) 49.29±8.40 years (range 30-72) for patients in the 'during-chemotherapy' group and 48.85±8.53 years (27-70) for patients in the 'after-treatment' group. Additional participant demographic and clinical characteristics are shown in Table 1. From baseline to 8 weeks, 21.1% of participants (n=8) were classified in the 'positive change' subgroup based on the EORTC-QLQ-C30 PF domain, whereas 78.9% (n=30) were classified in the 'unchanged' subgroup for patients during-chemotherapy. Overall, 51.4% of participants (n=38) were classified as exhibiting a 'positive change', whereas 48.6% (n=36) were classified as 'unchanged' for patients in the after-treatment group. There were no significant differences between the levels of moderate and

vigorous physical activity between the 'positive change' and 'unchanged' subgroups in the during-chemotherapy group, and between the 'positive change' and 'unchanged' subgroups in the after-treatment group within the time periods (Table 1).

Changes in the 6MWT distance and the PF domain between the two time points

In the during-chemotherapy group, in the 'positive change' subgroup, the mean difference in the 6MWT walked distance between the baseline and the 8-week follow-up was +100.1 (90.2) m; in the 'unchanged' subgroup, the mean difference between timepoints was -7.00 (86.9) m, with p=0.004; F=0.004. In the after-treatment group, in the 'positive change' subgroup, the mean difference in the 6MWT walked distance between the baseline and the 8-week follow-up was +85.1 (83.0) m, and in the 'unchanged' subgroup, the mean difference between time points was +46.8 (75.1) m, with p=0.043; F=0.292 (Figure 2A and 2B).

Test rest reliability of the 6MWT distance from test to retest

The test-retest reliability of the 6MWT distance was moderate in the during-chemotherapy group, with an ICC= 0.746 (95.0% CI: 0.51-0.86), and excellent in the

Table 1: Demographic and clinical characteristics of the groups.

Characteristic	During-chemotherapy		p	After-treatment	
	Positive change group (n= 8)	Unchanged group (n= 30)		Positive change group (n= 38)	Unchanged group (n= 36)
	Sociodemographic characteristics				
Age (year), mean±SD	47.75±6.60	49.70±8.78	.563	47.03±9.02	50.78±8.00
Education n (%)			.099		
Basis	4 (50)	12 (40)		15 (39.5)	17 (47.2)
Medium	0 (0)	11 (36)		11 (28.9)	11 (30.6)
Superior	4 (50)	7 (23.3)		12 (31.6)	8 (22.2)
Occupation, n (%)			.905		
Home duties	2 (25)	7 (23.3)		13 (34.2)	16 (44.4)
Full time	2 (25)	5 (16.7)		5 (13.2)	6 (16.7)
Temporary sick leave	0 (0)	1 (3.3)		12 (31.6)	11 (30.6)
Permanent sick leave	4 (50)	17 (56.7)		8 (21.1)	3 (8.3)
Smoking status n (%)			.663		
Never smoker					
Current smoker	4 (50)	11 (36.7)		20 (52.6)	19 (52.8)
Ex-smoker	1 (12.5)	8 (26.7)		7 (18.4)	5 (13.9)
	3 (37.5)	11 (36.7)		11 (28.9)	12 (33.3)
Alcohol intake, n (%)			.863		
Never					
Monthly	4 (50)	12 (40)		19 (50)	15 (41.7)
Weekly	2 (25)	7 (23.3)		6 (15.8)	7 (19.4)
Daily	2 (25)	9 (30)		11 (28.9)	14 (38.9)
	0 (0)	2 (6.7)		2 (5.3)	0 (0)
	Clinical characteristics				
Cancer stage, n (%)			.141		
I	3 (37.5)	8 (26.7)		17 (44.7)	8 (22.2)
II	1 (12.5)	15 (50)		16 (42.1)	23 (63.9)
III	4 (50)	7 (23.3)		5 (13.2)	5 (13.9)
Medical treatment, n (%)			.421		
No treatment	2 (25)	4 (13.3)		0 (0)	0 (0)
Radiotherapy	0 (0)	0 (0)		1 (2.6)	1 (2.8)
Chemotherapy	6 (75)	26 (86.7)		2 (5.3)	2 (5.6)
Radiotherapy & chemotherapy	0 (0)	0 (0)		35 (92.1)	33 (91.7)
Menopause, n (%)	5 (62.5)	17 (56.7)	.767		
No	3 (37.5)	13 (43.3)		5 (13.2)	2 (5.6)
Yes				33 (86.8)	34 (94.4)
Accelerometry (MVPA, min/week) mean±SD	84.92±33.04	84.41±38.81	.974	77.41±27.18	74.97±34.04
Body Mass Index, (kg/m^2) mean±SD	24.65±4.69	27.46±4.26	.113	26.11±5.72	28.30±5.80

P values of between-group differences using *t*-test for independent samples (continuous variables) and X^2 analysis

(categorical variables). n = sample size. SD: standard deviation. MVPA: moderate-vigorous physical activity per week.

Fig.2A Change in the 6MWT distance (m) between baseline and 8 weeks tests in the 'positive change' and the 'unchanged' subgroups from the during-chemotherapy group.
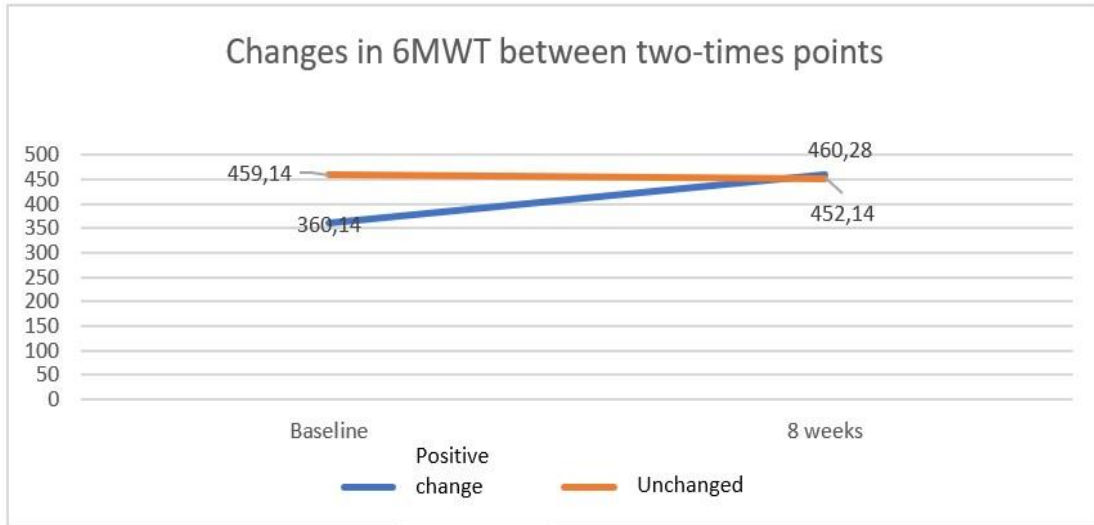
Fig.2B Change in the 6MWT distance (m) between baseline and 8 weeks tests in the 'positive change' and the 'unchanged' subgroups from the after-treatment group.
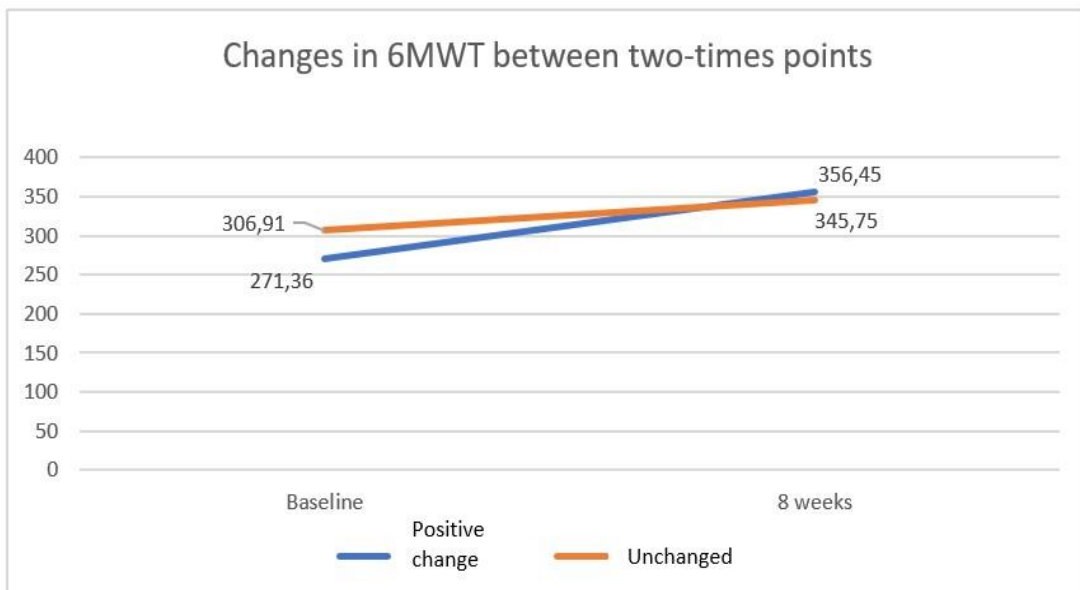
after-treatment group, with an ICC= 0.934 (95.0% CI: 0.89-0.95).

MCID calculation – anchor-based approach

The areas under the receiver operating characteristic (AUROC) curves were .808 (p=.008, 95.0% CI 0.63-0.98; Figure 3A) in the during-chemotherapy group and .646 (p=.032, 95.0% CI .52-.77; Figure 3B) in the

Fig.3A The Area Under Receiver Operating Characteristic (AUROC) curve
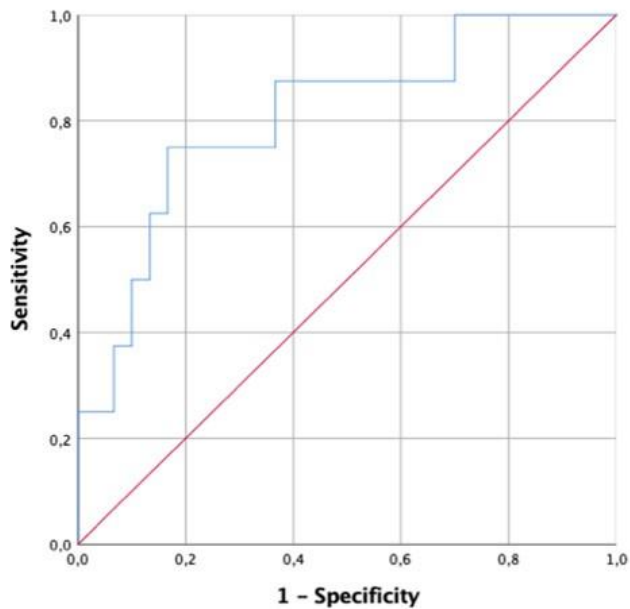
Fig. 3B The Area Under Receiver Operating Characteristic (AUROC) curve
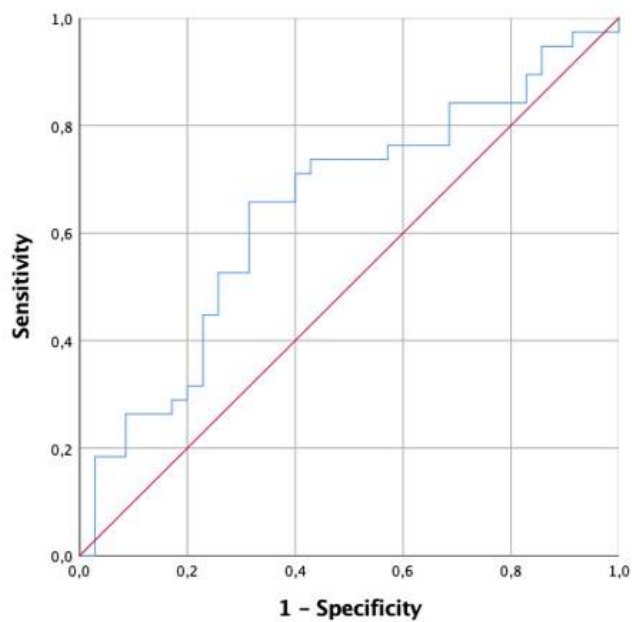
after-treatment group. The optimal cut-off

50

points for clinically relevant decline were -58.9 m (with a sensitivity of 87% and a specificity of 70%) and -42.7 m (with a sensitivity of 97% and a specificity of 91%), respectively.

MCID calculation – distribution-based approach

The distribution-based methods calculated for the during-chemotherapy and after treatment groups showed MCID estimates of 66.5 m and 41.4 m based on SEM and of 41.5 m and 40.5 m based on ES, respectively.

DISCUSSION

The results of this study have important clinical applications, as we have established a minimum distance for the 6MWT using a treadmill. We determined cut-off points in order to have reference values in active women with breast cancer during and after medical treatments, expanding the possibilities of the use of the 6MWT to improve the monitoring and evaluation of physical health status. The reliability of the 6MWT distance was moderate and excellent in the during-chemotherapy and in the after-treatment group respectively. We have estimated that changes between 41 and 66 m for women in the during-chemotherapy group and between 40 and 42 m for women in the after-treatment group in the 6MWT distance on a treadmill

indicates a significant clinical improvement. Women with breast cancer may experience adverse side effects associated with cancer diagnosis and treatments, which can lead to significant physical function deterioration [36] that has been related not only to a decrease in health status [37] but also to increased risks of recurrence and mortality [38]. For these reasons, researchers must have valid reference values to identify changes in patients' health [39].

The range of MCID for the 6MWT in chronic diseases has been established as 14 to 30.5 m [10]. However, previous evidence in different populations suggests that it is possible to find higher values, up to 58.5 m, in patients with idiopathic pulmonary fibrosis [40,41] and even 167 m in women with fibromyalgia [42]. The values we report may provide an indication of the MCID for the 6MWT in patients with cancer; however, it is clear that the MCID must be set for each specific condition [43]. ranges of previous studies conducted in lung cancer [10,12] showed MCID14 to 42 m in studies using an overground 6MWT. The wide range of MCIDs may be explained by factors such as methodologies to calculate the MCID score, anchors used, levels of physical fitness, demographic characteristics, or the instrument used [43]. Although the previous results could be an approximate reference, more specific values are required for the use of the

treadmill in the 6MWT for patients with breast cancer.

The American Thoracic Society (ATS) does not recommend the use of a treadmill when conducting the 6MWT [44]; however, this advice was based on the result of only one study [45]. Subsequent evidence is not in agreement concerning the reliability of the 6MWT on a treadmill compared to overground [19]. Despite the ATS guidelines, the 6MWT on a treadmill has been used in subsequent trials [18–20,45] to assess functional exercise capacity and to compare with reference values for the 6MWT overground. More evidence on the reliability of reference values for the 6MWT on a treadmill is required across different clinical populations.

According to previous studies [12,40,41,46], our results report a wide MCID range in the during-chemotherapy group, although the values were very similar to the references established for the 6MWT in a corridor. This large difference in values could be due to the impact on physical function while these women are receiving treatment [47] and may be due to the use of both anchor- and distribution-based methods. The two methods were frequently used together in previous studies to calculate the MCID for the 6MWT [9,32,40,41,46,48–52]; additionally, we used an increase ≥5 points in the PF domain of the EORTC-QLQ-C30,

which has been widely accepted for its ability to determine physical improvement [53]. This method considers the importance of the change but is sensitive to the degree of variability in the sample, which was large in this group. With our results, it may be adequate to think that MCIDs of approximately 54 m in the during-chemotherapy group and 41.5 m in the after-treatment group are appropriate minimum improvement points for monitoring physical health.

The MCID helps both clinicians and researchers interpret changes in health status objectively, but our study also enables the detection of physical deterioration, a risk factor for poor health, recurrence, and mortality in patients with cancer [54]; thus, it has important clinical and research implications. In addition, identifying patients with physical deterioration and providing them with supportive programs may be useful for determining sample sizes in research studies, establishing new research designs, selecting variables or assessing the effectiveness of new approaches. Additionally, it is important to note that obtaining a reference value, such as the MCID, is necessary for a continuously growing clinical population, such as women with breast cancer. In a clinical context, the use of a treadmill provides a logistical

advantage since it is often difficult to find a hallway that is free of distractions.

Limitations

This study has several limitations. One of these is the use of a treadmill for the 6MWT. We know that the main limitation is the inadequacy of the comparison with the values of previous studies conducted in corridors, but we believe that the treadmill is a widely used resource in clinical situations. In addition, the participants of the studies analysed were part of clinical trials with different interventions, although there were no differences between the groups in terms of the level of moderate and intense physical activity that they performed, as measured with accelerometery. Also, an important limitation to consider is that in some subgroups the sample size is limited that could lead to higher bias in the results, therefore, they should be interpreted with caution. These results are derived from active women with breast cancer, so they may not be extrapolated to all breast cancer patients. More studies are needed to confirm these results in women with breast cancer.

In conclusion, our study showed the MCID of the 6MWT distance, when conducted on a treadmill, in women with breast cancer is between 41 and 66 m in patients undergoing active treatment and between 40 and 42 m in patients after completion of treatment. These values could be used by clinicians and researchers as reference data to interpret changes in the physical health status of active patients with breast cancer when using the 6MWT on treadmill.

Conflict of interest

The authors declare no conflict of interests

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STUDY II

COLORECTAL CANCER PAIN UPON DIAGNOSIS AND AFTER TREATMENT: A CROSS-SECTIONAL COMPARISON WITH HEALTHY MATCHED CONTROLS

Supportive Care in Cancer

2022

STUDY II. COLORECTAL CANCER PAIN UPON DIAGNOSIS AND AFTER TREATMENT: A CROSS-SECTIONAL COMPARISON WITH HEALTHY MATCHED CONTROLS

ABSTRACT

Background: The current study sought to explore whether cancer pain (CP) already exists in patients at colorectal cancer (CRC) diagnosis before treatment compared with patients with colorectal cancer (CRC) after treatment and a healthy matched control group. The study also sought to examine whether factors related to physical health status could enhance pain processes.

Methods: An observational cross-sectional study was conducted following the STROBE checklist. Twenty-nine newly diagnosed and forty post-treatment patients with CRC and 40 healthy age/sex-matched controls were included for comparison. Pain, local muscle function, and body composition outcomes were assessed by a physiotherapist with > 3 years of experience. ANCOVA and Kruskal–Wallis tests were performed, with Bonferroni and Dunn-Bonferroni post hoc analyses and Cohen's d and Hedge's effect size, as appropriate.

Results The analysis detected lower values of pressure pain threshold (PPT) points, the PPT index, and abdominal strength and higher values of self-reported abdominal pain in newly diagnosed patients, with even more marked results observed in the post-treatment patients, where lower lean mass and skeletal muscle index values were also found than those in the healthy matched controls ($p < 0.05$). In the post-treatment and healthy matched control groups, positive associations were observed between the PPT lumbar dominant side points and abdominal isometric strength and lean mass, and negative associations were observed between the lumbar dominant side points and body fat ($p < 0.05$).

Conclusion: Upon diagnosis, patients with CRC already show signs of hyperalgesia and central sensitization and deteriorated physical conditions and body composition, and this state could be aggravated by subsequent treatments.

INTRODUCTION

Cancer pain (CP) is one of the most prevalent and concerning aspects of the disease that patients with cancer must face, and it occurs in more than 60% of patients across all cancer stages[1], even from diagnosis[2]. This pain is very difficult to manage because it is a poorly understood and undertreated syndrome[3] that involves crucial health expenditures[4].

A systematic classification of chronic pain was developed by the International Association for the Study of Pain (IASP) that distinguishes chronic primary and chronic secondary pain syndromes. When pain persists or recurs for more than 3 months, it is considered chronic pain. In some conditions where pain may be considered a disease, the term chronic primary pain is used. However, in other cases, pain is secondary to an underlying disease, such as chronic cancer-related pain[5]. Additionally, the term central sensitization is defined by IASP as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input". Clinically, sensitization may only be inferred indirectly from phenomena such as hyperalgesia or allodynia[6].

The presentation of chronic pain and central sensitization in patients with colorectal cancer (CRC) in the survival phase is well established[7, 8]. This abnormal processing of nociceptive inputs decreases the pressure pain threshold (PPT)[9]; therefore, low PPT in local and distant areas of cancer reflects primary hyperalgesia and central sensitization, which can increase perceived pain[10]. Depending on its pathogenesis, CP physiopathology may be of nociceptive, neuropathic, mixed or psychogenic origin. After treatment, a state of central sensitization is increased in 75% of patients with CRC compared with that in healthy matched controls[8]. Among the possible factors influencing this state are cancer treatments, such as surgery[11], chemotherapy and radiotherapy[8, 12, 13]; a state of prolonged nociceptive or neuropathic pain[14]; other factors related to muscle and adipose tissue that are closely related to CP[8, 15]; and certain behaviors in patients, such as kinesiophobia [16], which may increase pain perception.

In patients newly diagnosed with CRC who did not undergo cancer treatment, abdominal pain may already be present[2]. Tumors themselves induce CP by constricting or invading surrounding tissue, inducing infection or inflammation, or releasing chemicals. Tumor-induced visceral (nociceptive, neuropathic or mixed) pain can also promote a central sensitization state[14]. However, the psychological distress of the impact of cancer diagnosis (which involves fear, anxiety, pain catastrophizing, and other

responses) influences central sensitization and may modulate pain[17] by increasing the level of systemic inflammation through activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system[18]. Additionally, these patients present factors related to unhealthy lifestyle habits that are risk factors for CRC appearance[19], which could also be factors that influence the early presentation of CP, as indicated in other populations[20, 21].

Although cancer treatment may induce pain, how this may be already established from the moment of diagnosis is unclear. Therefore, it would be interesting to fully elucidate this early CP appearance to offer tailored interventions to prevent or mitigate CP. Therefore, the current study sought to explore whether CP already exists in patients with CRC upon diagnosis before cancer treatment compared with patients after treatment and a healthy matched control group. The study also sought to examine whether factors related to the physical health status could influence pain processes.

METHODS

Study design and participants

We conducted an observational cross-sectional study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist[22]. For this study, the baseline evaluation of two cohorts (newly diagnosed n=29; posttreatment n=40) and 40 healthy age/sex-matched controls were included for comparison. Healthy age/gender-matched controls were recruited through announcements by the University of Granada on social networks. Both previous cohorts had the following inclusion criteria: 1) patients of legal age (>18 years), 2) patients diagnosed with CRC (stage I to IIIa), 3) patients on a waiting list for surgery (newly diagnosed study), or 4) patients completed their medical treatment (posttreatment group). Patients with any medical contraindication or musculoskeletal condition to perform the assessments (e.g., chronic lumbar pain, fibromyalgia, or osteoarthritis), any abdominal surgery, or any previous cancer treatment (newly diagnosed group) were excluded. After the first contact, the patients were contacted by telephone for an appointment at the Sport and Health Research Center or Physiotherapy Laboratory of the Health Science Faculty of the University of Granada. All the participants signed an informed consent form before participating in the study.

The study protocols were approved by the Research Ethics Committee of the University of Granada (0572-M1–16 and 1087-N-16), and the study was performed in accordance with Law 14/2007 on

Biomedical Research and the guidelines of the World Medical Association Declaration of Helsinki.

Outcomes

The same evaluation protocols and assessment instruments (model and brand) were used in all the participants. Evaluations were made by a trained researcher with experience in the evaluation of patients with a CRC >3 years. The patients were asked if they had taken any rescue analgesics in the last 24 hours, if so, assessment could be postponed. The demographic and clinical details were entered from the medical reports of the patients.

Pain

Pressure pain thresholds (PPT) (kilopascals, kPA): Testing was performed using an electronic algometer (Somedic AB. Farsta., Sweden) at the dominant and nondominant lumbar, supraumbilical, infraumbilical and second metacarpal points, with a perpendicular diameter of 1 cm (absolute value). At each point, the evaluation was performed three times with a rest of 30 seconds, and progressive increases in force (30 kPA/sec) were applied until the first perception of change from pressure to pain, which was previously explained to the participants. The mean of three rounds was registered as a unidimensional variable with

an intraclass correlation coefficient (ICC) of .91[23]. Similarly, the "PPT index" (relative PPT value) was calculated in patients with CRC and shows the degree of sensitivity (%)[12]. This index is obtained by dividing the mean of each PPT point from patients by the mean of each PPT point in the healthy matched control group (HMCG). CRC patients with a higher PPT index were most consistent with HMCG. A difference of 20% between groups was considered clinically significant[24].

Self-report of spontaneous pain: Patients were asked to rate their pain intensity in the abdominal and lumbar areas using a horizontal visual analog scale (VAS) of 10 centimeters (cm), where 0 means "no pain" and 10 means "the worst pain." This instrument has an ICC of .97[25]. The cutoff scores for musculoskeletal pain were as follows: mild pain (0 to 3 points), moderate pain (3 to 6 points), and severe pain (>6 points) [26].

Abdominal Isometric Strength

Abdominal isometric strength was assessed using the trunk curl test to evaluate a possible alteration of the lumbopelvic functional stability. From a supine position with flexion of the knees and hips, patients flexed their trunk to separate the lower angle of the scapula from the stretcher and then maintained this position, with their arms extended without touching their

knees as long as they could. Time was recorded up to a maximum of 90 seconds. This test has a high reliability (ICC >0.97) [26].

Muscle structure

Muscle images were captured using an ultrasound device (MyLab 25; Esaote Medical System, Genova, Italy) for the multifidus, transversus abdominis, and external and internal obliques (cm). A 12 MHz linear probe was used following a previous protocol[8]. The images were recollected at a depth of 5 cm with the patient lying on the stretcher during apnea. The reliability of the ultrasound images for multifidus (ICC=0.55–0.86) and abdominal (ICC>0.81) muscle thickness has been previously shown[27].

Body composition and anthropometry

Body composition (musculoskeletal mass (kg), body fat (%), body mass index (BMI, kg/m2), and skeletal muscle mass index (musculoskeletal mass/height 2 (kg/m2)) were obtained using an InBody 720 tetrapolar eight-point tactile electrode system (Biospace Co., Ltd., Seoul, Korea). The patients were instructed to rest (no rigorous exercises in the previous 24 hours) without a meal/water 3 hours before measurement. The cutoff points related to a higher risk of CRC are a weight of 82 kg and a BMI of 31 kg/m2 [33]. The skeletal muscle

mass index is based on physical disability risk and has been used as a usual cutoff to define moderate sarcopenia when it is between 8.51 and 10.75 kg/m2 (men) or 5.76 and 6.75 kg/m2 (women)[28].

Waist circumference (cm) was assessed using plastic tape at the end of exhalation at the midpoint between the lowest rib and iliac crest. A value of 87 cm is associated with a higher risk of CRC[29].

Statistical Analysis and data presentation

Analyses were performed using the SPSS statistical package for MacOS Sierra version 10.13 (IBM Corp. iReleased 2016, 24.0 version, Armonk, NY: IBM Corp.), with a level of significance of $p<0.05$ and a 95% confidence interval (CI). The results are expressed as means (m) ± standard deviation (SD) for continuous variables or numbers (n) and percentages (%) for category variables. The Shapiro Wilk test was used to check the normal distribution of the outcomes ($p>0.05$). Analysis of variance (ANOVA) was performed to assess the similarity between groups for continuous variables related to demographic and clinical characteristics. Chi squared ($\chi2$) test was used for category variables. Three-way analysis of covariance (ANCOVA) was used to evaluate the between-group difference in outcomes with a normal distribution, with ages, stages and

cancer treatment as covariables. Post hoc analysis was performed with the Bonferroni test, and Cohen's d effect size was calculated to quantify the between-group differences considered small (.20), moderate (.50), and large (.80). The Kruskal-Wallis test was used when the outcomes did not reach normality, and post hoc comparisons were performed using the Dunn-Bonferroni post hoc method. Hegde's effect size was calculated to quantify the between-group differences, which were considered small (.20), moderate (.50), and large (.80). Additionally, Pearson's test was used to analyze the bivariate correlation between the dominant lumbar side of the PPT and the remaining dependent outcomes in each group. A correlation from 0 to 0.25 indicates an absent or weak relationship, a correlation from 0.25 to 0.50 indicates a fair relationship, a correlation from 0.50 to 0.75 indicates a moderate to good relationship, and a correlation greater than 0.75 indicates a very good relationship[30]. Missing data were not included in the analysis.

RESULTS

Of the 239 screened patients, 110 were eligible to complete the assessment. The reasons for ineligibility included participation declination (n=76), not meeting the inclusion or exclusion criteria (n=46), and failure in the assessment

instruments (n=7). Finally, 29 patients (69.0% men) with an average age of 61.68⬜12.78 years were included in the newly diagnosed group (NDG), 40 patients (65.0% men) with an average age of 60.80⬜10.02 years were included in the posttreatment group (PTG), and 40 healthy matched people (52.5% men) with an average age of 59.54⬜9.69 years were included in the HMCG. The demographic and clinical characteristics of each participant group are shown in Table 1.

Pain

Figure 1 shows the PPTs differences between groups. ANCOVA detected significant differences between groups at all PPT evaluation points: lumbar side (dominant; F=5.4, p=0.006; nondominant; F=12.2, p<0.001), supraumbilical side (dominant; F=10.8, p<0.001; nondominant; F=10.8, p<0.001), infraumbilical side (dominant; F=7.8, p=0.001; nondominant; F=8.0 p=0.001) and second metacarpal side (dominant; F=5.5, p=0.005; nondominant; F=7.7, p=0.001). The NDG and PTG registered lower values than the HMCG and were always lower in the PTG. The intergroup effect size between the NDG and PTG was large for the supraumbilical dominant side (d=0.81; CI=0.29, 1.32) and moderate for the lumbar nondominant side (d=0.57; CI=0.07, 1.06), supraumbilical nondominant side (d=0.57; CI=0.07, 1.07),

Table 1 Demographic and clinical characteristics of the groups

		Newly diagnosed ($n = 29$)	Post-treatment ($n = 40$)	Healthy matched control ($n = 40$)	p value
Age (years) m ± SD		61.68 ± 12.78 1	60.80 ± 10.02	59.54 ± 9.69	0.712
Time since surgery (months) m ± SD		-	13.26 ± 8.76	-	-
Gender n (%)	Male	20 (69.0)	26 (65.0)	21 (52.5)	0.323
	Female	9 (31.0)	14 (35.0)	19 (47.5)	
Social situation n (%)	Single	2 (6.9)	3 (7.5)	2 (5.0)	0.101
	Married	22 (75.9)	34 (85.0)	30 (75.0)	
	Divorced	1 (3.4)	1 (2.5)	7 (17.5)	
	Widowed	4 (13.8)	2 (5.0)	1 (2.5)	
Smoking status n (%)	Never smoked	13 (44.8)	20 (50.0)	20 (50.0)	0.988
	Current smoker	3 (10.3)	4 (10.0)	4 (10.0)	
	Ex smoker	13 (44.8)	16 (40.0)	15 (37.5)	
Alcohol intake n (%)	Never	15 (51.7)	15 (37.5)	14 (35.0)	0.330
	Monthly	4 (13.8)	9 (22.5)	6 (15.0)	
	Weekly	2 (6.9)	9 (22.5)	11 (27.5)	
	Daily	8 (27.6)	7 (17.5)	7 (17.5)	
Physical activity level n (%)	< 10 MET/h w	2 (7.7)	5 (12.5)	3 (8.3)	-
	> 10 MET/h week	24 (92.3)	35 (87.5)	33 (91.7)	
Cancer stage n (%)	I	5 (17.2)	0 (0.0)	-	-
	II	5 (17.2)	14 (35.0)	-	
	III	16 (55.2)	25 (62.5)	-	
Medical treatment	No treatment	29 (100)	8 (20.0)	40 (100)	-
	Radiotherapy	-	3 (7.5)	-	
	Chemotherapy	-	16 (40.0)	-	
	Radiotherapy and chemotherapy	-	13 (32.5)	-	

p values of between-group differences using ANOVA test for independent samples (continuous variables) and X^2 analysis (categorical variables). m, mean; n, sample size; SD, standard deviation; % (percentage). *$p < 0.05$; **$p < 0.001$
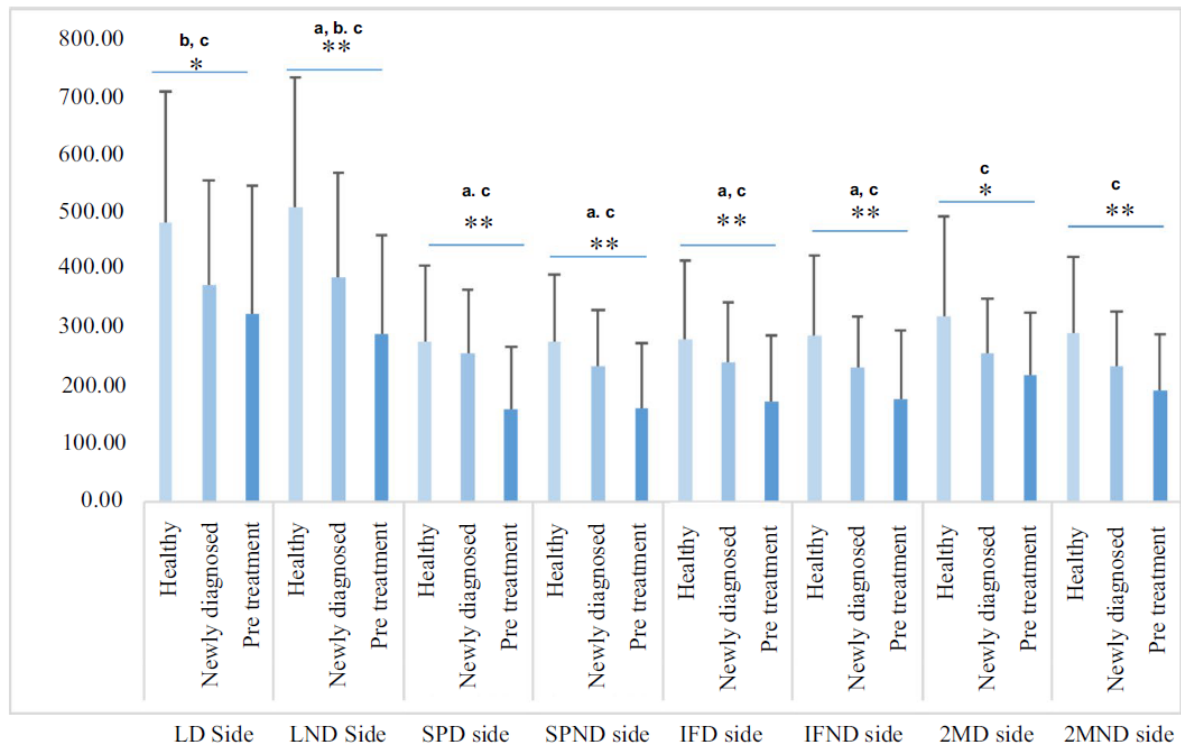
Fig. 1 Pressure pain thresholds (kPa) between-groups differences. *$p < 0.05$; **$p < 0.001$; a—between newly diagnosed and post-treatment groups differences with Bonferroni post hoc; b—between newly diagnosed and healthy matched control groups differences with Bonferroni post hoc; c—between post-treatment and healthy matched control groups differences with Bonferroni post hoc. LD side, lumbar dominant side; LND side, lumbar nondominant side; SPD side, supraumbilical dominant side; SPND side, supraumbilical nondominant side; IFD side, infraumbilical dominant side; IFND side, infraumbilical nondominant side; 2MD side, second metacarpal dominant side; 2MND side, second metacarpal nondominant side

infraumbilical dominant side (d=.61; CI=0.11, 1.10) and infraumbilical nondominant side (d=0.51; CI=0.01, .99). The intergroup effect size between the NDG and HMCG was moderate for the dominant lumbar side (d=0.52; CI=0.01, 1.01) and nondominant lumbar side (d=0.58; CI=0.07, 1.07). The intergroup effect sizes between the PTG and HMCG were large for the nondominant lumbar side (d=1.11; CI=0.61, 1.57), supraumbilical points (dominant side: d=0.98, CI=0.49, 1.44; nondominant side: d=1.01, CI=0.52, 1.47), infraumbilical points (dominant side: d=0.86, CI=0.38, 1.32; nondominant side: d=0.86, CI=0.37, 1.32) and second metacarpal nondominant side (d=0.86; CI=0.38, 1.32) and moderate for the lumbar dominant side (d=0.71; CI=0.23, 1.16) and second metacarpal nondominant side (d=0.70; CI=0.22, 1.16). ANCOVA with cancer stage as a covariate influenced the results on the lumbar side (dominant p=0.217; nondominant p=0.631) and infraumbilical side (dominant p=0.650; nondominant p=0.128).

ANCOVA of the PPT index revealed the number of patients with significant clinical differences (>20%) relative to the HMCG values for the lumbar dominant side (n=14, 50.0% in the NDG; n=27, 67.5% in the PTG), lumbar nondominant side (n=16, 57.1% in the NDG; n=29, 72.5% in the PTG), supraumbilical dominant side (n=12, 41.3% in the NDG; n=31, 77.5% in the PTG),

supraumbilical nondominant side (n=14, 50.0% in the NDG; n=31, 77.5% in the PTG), infraumbilical dominant side (n=13, 46.4% in the NDG; n=30, 75.0% in the PTG), infraumbilical nondominant side (n=14, 50.0% in the NDG; n=26, 65.0% in the PTG), second metacarpal dominant side (n=15, 53.5% in the NDG; n=27, 67.5% in the PTG) and second metacarpal nondominant side (n=17, 66.7% in the NDG; n=27, 67.5% in the PTG). Figure 2 shows PPT index differences between NDG and PTG.

The Kruskal-Wallis test of self-reported spontaneous pain revealed a significant difference between groups in abdominal pain (p=0.006). Figure 3 shows differences in VAS (cm) at the abdominal and lumbar areas between groups. The post hoc analysis identified significant differences between the NDG and HMCG (p=0.005). The intergroup effect size was moderate (g=0.90; CI=0.39, 1.40) between these groups (Figure 3). No significant differences were found in lumbar pain (p=0.920).

Abdominal isometric strength

The Kruskal-Wallis test revealed a significant difference (p<0.001) between groups for abdominal isometric strength, with lower values in the NDG and PTG than in the HMCG. Post hoc analysis identified significant differences between the NDG and HMCG (p=0.011) and between the PTG and HMCG (p<0.001). Table 2 shows

68
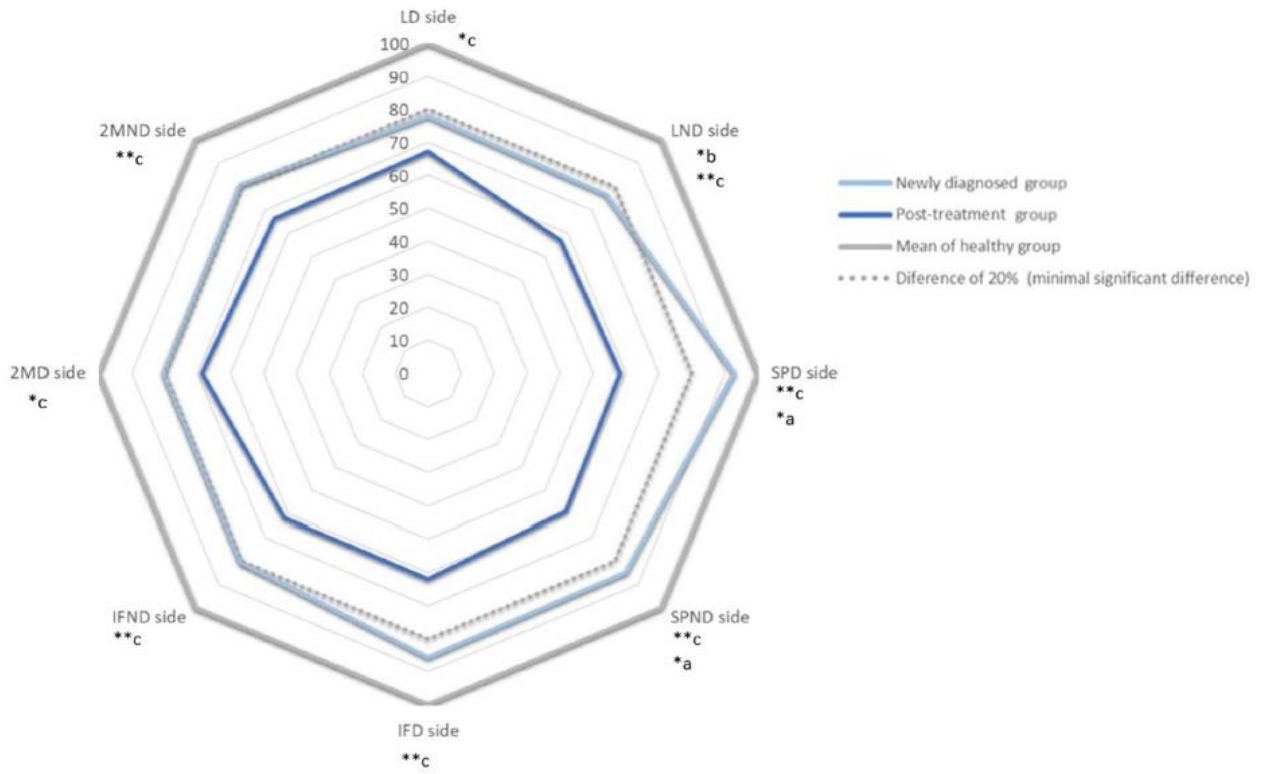
Fig. 2 Pressure pain threshold index differences between newly diagnosed and post-treatment groups. *$p < 0.05$; **$p < 0.001$; a—between newly diagnosed and healthy matched control group differences with Bonferroni post hoc; b—between healthy matched control and post-treatment groups differences with Bonferroni post hoc; c—between newly diagnosed and post-treatment groups differences with Bonferroni post hoc; LD side, lumbar dominant side; LND side, lumbar nondominant side; SPD side, supraumbilical dominant side; SPND side, supraumbilical nondominant side; IFD side, infraumbilical dominant side; IFND side, infraumbilical nondominant side; 2MD side, second metacarpal dominant side; 2MND side, second metacarpal nondominant side

Fig. 3 Between groups differences in VAS (cm) at abdominal and lumbar area. HMCG, healthy matched control group; NDG, newly diagnosed group; PTG, post-treatment group. *$p < 0.05$ with the Kruskal–Wallis test

comparisons between groups according to the abdominal isometric strength.

Muscle structure

The Kruskal-Wallis test showed a significant difference in the width of the lumbar multifidus (p<0.002) between groups, with lower values in the NDG and PTG than in the HMCG. Post hoc analysis identified significant differences between the NDG and HMCG (p=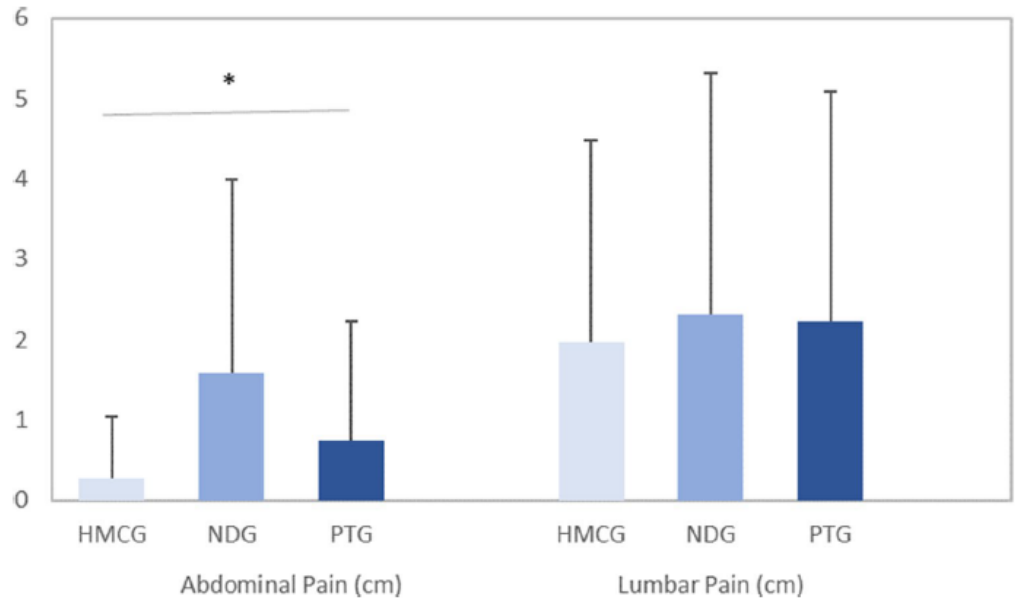0.011) and between the PTG and HMCG (p=0.004). Table 2 shows the comparison between groups according to muscle structure.

Body composition and anthropometric outcomes

ANCOVA of musculoskeletal mass data revealed a significant difference between groups (F=3.14; p=0.047), with lower values in the PTG than in the NDG and HMCG. Bonferroni post hoc analysis identified significant differences between the NDG and PTG (p=0.014; CI=0.76, 6.65). Additionally, Kruskal-Wallis test showed a significant difference between groups for the skeletal muscle mass index (p=0.038). Post hoc analysis identified significant differences between the NDG and PTG (p=0.042). No significant differences were found for the remaining variables. Table 2 shows comparisons between groups according to body composition and anthropometric outcomes.

70

Correlations

In all groups, Pearson's test showed a significant positive association (p<0.001) between the dominant lumbar side point and remaining PPT points. In the PTG and HMCG, positive associations were observed between the dominant lumbar side points and abdominal isometric strength (rs=0.471 and p=0.002 in the PTG; rs=0.501 and p=0.003 in the HMCG) and musculoskeletal mass (rs=0.320 and p=0.044 in the PTG; rs=0.548 and p=0.001 in the HMCG). Additionally, negative associations were observed between the dominant lumbar side points and body fat (rs=-0.390 and p=0.013 in the PTG; rs=-0.429 and p=0.010 in the HMCG). Figure 4 shows a schematic representation of the bivariate correlation between the lumbar dominant side of the PPT and remaining dependent outcomes in each group.

DISCUSSION

We found that CP is already present in CRC patients at diagnosis prior to treatment. The analysis detected a threshold reduction in most PPT points, lower values in the PPT index, higher self-reported abdominal pain, and lower abdominal strength in newly diagnosed patients, with even more marked results in posttreatment patients, where lower lean mass and skeletal muscle index values were also found compared with those in the healthy matched controls.

Table 2 Comparison between groups

		m	SD	95% CI	Effect size	95% CI	p value
Abdominal isometric strength							
Trunk curl test (s)	Newly diagnosed	42.11	34.86	28.85, 55.37	0.60 b	0.10, 1.10	**<0.001***¥ b,c**
	Post-treatment	24.89	10.92	21.39, 28.38	1.49 c	0.98, 1.99	
	Healthy matched control	62.65	34.15	51.26, 74.04			
Muscle structure							
Width lumbar multifidus (cm)	Newly diagnosed	3.75	.68	3.49, 4.01	0.84 b	0.33, 1.36	**<0.001**¥ b, c**
	Post-treatment	3.55	1.01	3.22, 3.87	0.88 c	0.41, 1.36	
	Healthy matched control	4.32	.65	4.10, 4.54			
Depth transversus abdominalis (cm)	Newly diagnosed	0.38	0.22	0.30, 0.47			0.339¥
	Post-treatment	0.35	0.15	0.30, 0.40			
	Healthy matched control	0.39	0.12	0.35, 0.43			
Depth external oblique (cm)	Newly diagnosed	0.63	0.31	0.51, 0.75			0.102¥
	Post-treatment	0.53	0.29	0.44, 0.62			
	Healthy matched control	0.65	0.33	0.54, 0.76			
Depth internal oblique (cm)	Newly diagnosed	0.55	0.29	0.44, 0.67			0.290¥
	Post-treatment	0.57	0.18	0.51, 0.63			
	Healthy matched control	0.65	0.27	0.56, 0.74			
Anthropometric and body composition outcomes							
Musculoskeletal mass (kg)	Newly diagnosed	30.63	6.63	28.05, 33.20	0.62 a	0.12, 1.10	**0.047* a**
	Post-treatment	26.91	5.48	25.16, 28.67			
	Healthy matched control	27.74	6.45	25.65, 29.84			
Body fat (%)	Newly diagnosed	31.95	10.83	27.75, 36.15			0.732
	Post-treatment	33.84	9.90	30.68, 37.00			
	Healthy matched control	33.21	8.70	30.39, 36.02			
Body mass index (kg/m²)	Newly diagnosed	29.90	5.32	27.84, 31.97			0.327
	Post-treatment	28.34	5.01	26.74, 29.94			
	Healthy matched control	28.07	5.27	26.36, 29.78			
Weight (kg)	Newly diagnosed	80.78	17.33	74.05, 87.50			0.279
	Post-treatment	75.63	12.59	71.60, 79.66			
	Healthy matched control	75.52	14.73	70.74, 80.29			
Skeletal muscle index (kg/m²)	Newly diagnosed	11.31	2.17	10.47, 12.15	0.71 a	0.21, 1.20	**<0.05*¥ a**
	Post-treatment	9.95	1.43	9.50, 10.42			
	Healthy matched control	10.21	1.65	9.65, 10.77			
Waist circumference (cm)	Newly diagnosed	101.00	12.70	95.98, 106.02			0.137
	Post-treatment	101.90	12.43	97.92, 105.87			
	Healthy matched control	96.16	12.58	91.62, 100.69			

Between-group differences on p values using ANCOVA test for independent samples or Kruskal–Wallis test (¥). m, mean; SD, standard deviation; *$p < 0.05$; **$p < 0.001$; a, between newly diagnosed and post-treatment groups differences with Bonferroni post hoc; b, between newly diagnosed and healthy matched control groups differences with Bonferroni post hoc; c, between post-treatment and healthy matched control groups differences with Bonferroni post hoc

71
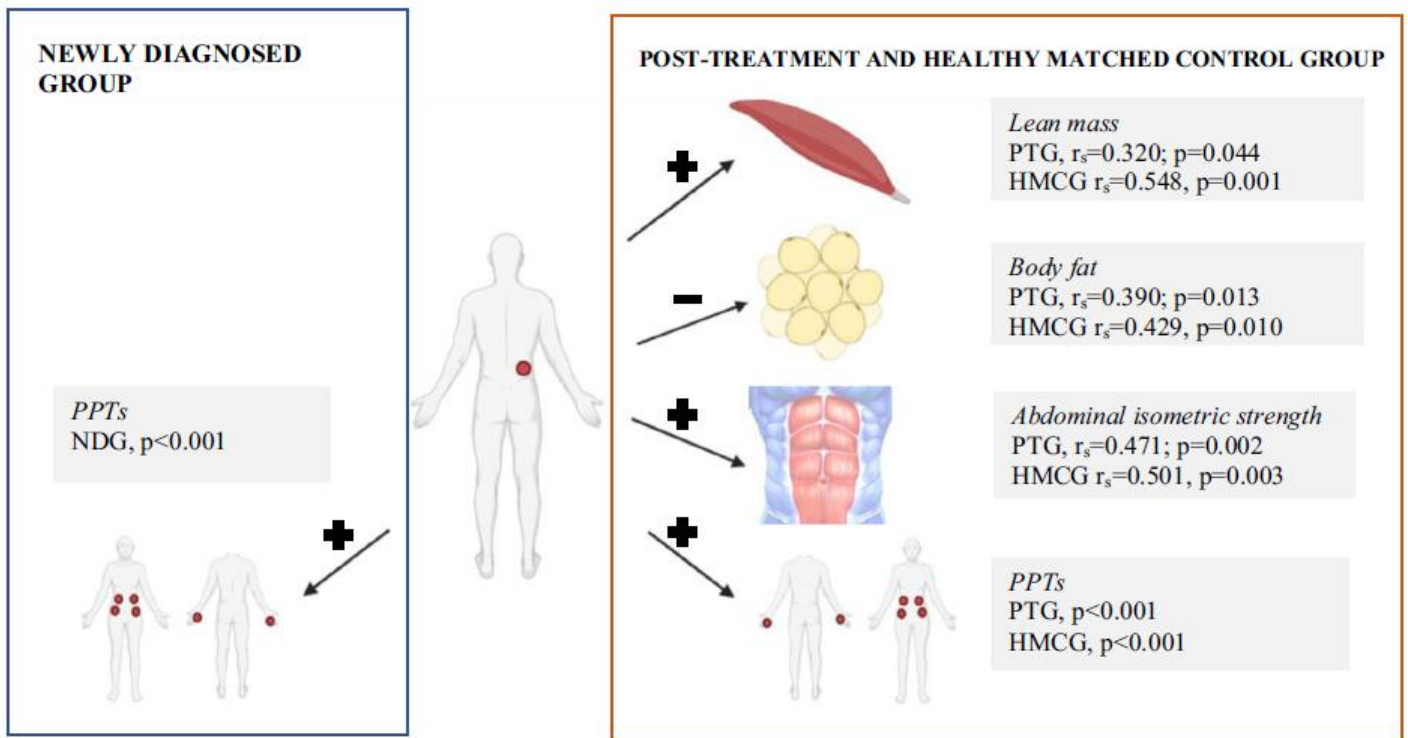
Fig. 4 Bivariate correlation between lumbar dominant side of pressure pain threshold and the rest of dependent outcomes in each group. Created in BioRender.com. + positive correlation; − negative correlation. LDS, lumbar dominant side; NDG, newly diagnosed group; PPTs, pressure pain thresholds; PTG, post-treatment group; HMCG, healthy matched control group

Curiously, our findings of a reduction in PPT suggest that from the moment of diagnosis, patients with CRC had CP, indicating the possible onset of central sensitization without the presence of some of the factors that may enhance CP in the posttreatment group. Additionally, 1 of 2 patients in the NDG showed a minimal clinical difference (>20%) in the PPT index compared with that in the HMCG. There are studies that address the issue of pain in newly diagnosed cancer patients, although their cohort is only partially treatment-naïve and it does not focus on patients with CRC. In the study by Ger LP et al.[31], a Taiwanese cohort of patients newly diagnosed with several types of cancer, including CRC, was analyzed.

They found that 38% (n=113) of the patients presented CP, and that only in 8% of those cases was due to cancer treatment. Also, they found that, among other reasons, pain prevalence correlated with patient socioeconomic characteristics (i.e., lower medical insurance coverage) and pain severity with a more advanced stage of the disease and previous inadequate pain management. In another study by Kelsen et al. [32], they analyzed data from newly diagnosed (64%), and just after their first chemotherapy (36%) patients with pancreas cancer. They found that there was a percentage having none (37%), mild (34%) or moderate-severe (29%) pain. Also, that their cohort presented less pain among the

preoperative patients, but also that there was a correlation between depressive symptoms and pain (which 38% of the cohort presented). These results could show the influence from both physiological and psychosocial dimensions of pain [33], which are sometimes present at diagnosis.

Additionally, the isometric strength values were 30% lower in the NDG and almost 60% lower in the PTG than in the HMCG, findings that are consistent with other study findings from our research group on PTG patients[34, 35]. The lower abdominal strength in NDG patients was a negative finding and shows the possible loss of muscle strength that often accompanies chronic pain[36]. Furthermore, the lumbopelvic area is the central area of the body where muscle chains are located[37, 38]. Functional alteration of the area could be related to a greater possibility of sacral fractures[39], joint instabilities[40], and low back pain[41, 42]. Additionally, previous evidence has shown that NDG early-stage patients with CRC already show muscle dysfunction, a phenomenon considered undetected in clinical practice but that shows a strong association with vital clinical end points, including survival and treatment toxicity[43]. Such findings could be used to start programs focused on strength exercises from diagnosis to try to mitigate the detrimental effects of future treatments on muscle strength.

Related to general muscle mass, the skeletal muscle mass index indicated that only the PTG showed moderate sarcopenia, a prevalent problem in patients with cancer because it involves a higher risk of developing immediate postoperative complications and decreased tolerance to chemoradiotherapy because of side effects[44]. However, in the muscles around the tumor, both the NDG and PTG presented a width reduction (with 13.19% less lumbar multifidus width in the NDG and 17.82% in the PTG) compared with the HMCG, a finding that is consistent with previous findings in patients with CRC[15, 45]. This early impact in muscle close to the tumor location could be caused by tumor inflammation-released cytokines[46]. Additionally, multifidus reduction may be related to overall survival[47], and its dysfunction is strongly associated with chronic low back pain[48].

Correlation analysis revealed that the PTG and HMCG were unexpectedly similar, with reductions in the dominant lumbar side PPT correlated with the remaining PPT points, lower values of isometric abdominal strength, lean mass, and higher body fat in both groups. Better muscle function may mitigate pain perception[49, 50]; additionally, a lower PPT is related to an excessive fat percentage, which is also associated with body biomechanical/structural changes,

increased inflammatory mediators, mood disturbance, poor sleep, and lifestyle issues[21], which may explain our findings. In the NDG, these correlations did not appear except for among the PPT points, and our algometry data in the NDG showed data dispersion. Therefore, we supposed that the wide range of variable responses might be due to the impact of the diagnosis. These findings highlight the importance of considering body composition, specifically increasing muscle and decreasing adipose tissue, in the pain management of these patients because it may indirectly affect their pain. In the case of newly diagnosed patients, body composition could help prevent this situation; however, additional studies are needed to clarify these findings.

Some limitations of our study should be noted. First, not all the factors that influence the development of central sensitization from the biopsychosocial perspective were analyzed in these patients; secondly, analyses with different groups limit the results, and no longitudinal changes could be studied; also, the study did not examine the presence of background pain or record any analgesic treatment therefore, these characteristics were not established as inclusion criteria to establish a representative sample of patients with CRC.

This study also presents some strengths. Widespread pain, which is a crucial objective measure was addressed. Also, this work attempts to respond to the limitations of a previous study in which prospective data from patients with CRC was needed to be obtained upon diagnosis[8]. Moreover, it highlights the deterioration of the health status at the time of diagnosis, thus reinforcing the need for multidisciplinary interventions that are necessary and must include, in addition to multimodal physical exercise interventions (endurance, resistance, strength, motor control, and flexibility, among others), educational, nutritional and psychosocial support interventions[51].

CONCLUSION

Before the start of cancer treatment, NDG patients with CRC show signs of primary hyperalgesia, central sensitization and deterioration in physical condition and body composition. Such symptoms appear to be further aggravated following cancer treatment. Hence, addressing the health status of these patients at diagnosis is crucial.

DECLARATIONS

Conflicts of interest

The authors declare no conflict of interest.

Availability of data and material

Data will be available upon request from the corresponding author.

Code availability

Not applicable.

Authors' contributions

ICV, MAM and AAO conceptualized the study and wrote the manuscript. PPM, MLG and AGS performed statistical analyses and wrote the manuscript. AMFP recruited and measured patients with cancer and healthy matched controls. AMFP and AAO created the database. All the authors analyzed and interpreted the data and revised and edited the manuscript for submission.

Ethics approval

The study protocols were approved by the Research Ethics Committee of the University of Granada (0572-M1-16 and 1087-N-16), and the study was performed in accordance with Law 14/2007 on Biomedical Research and the guidelines of the WMA Declaration of Helsinki.

Consent to participate

All the participants were informed verbally and in writing before signing the informed consent form.

Consent for publication

Not applicable.

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STUDY III

CARDIOTOXICITY AND THERAPEUTIC EXERCISE IN BREAST CANCER: EFFECTS AND DOSE. SYSTEMATIC REVIEW AND META-ANALYSIS

(Under Review in Scientific Reports)

STUDY III. CARDIOTOXICITY AND THERAPEUTIC EXERCISE IN BREAST CANCER: EFFECTS AND DOSE. SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Background: The effect of physical exercise in humans and which dose is the most appropriate for mitigating cardiotoxicity remain unclear.

Objective: to analyze the effects of therapeutic exercise in the management of oncology treatment-induced cardiotoxicity in women diagnosed with breast cancer (BC) and to identify the optimal dose of exercise.

Methods: A systematic search in PubMed, Web of Science, Scopus, CINAHL and Cochrane Library yielded 433 articles from inception to 30th August 2020.

Study selection: Randomized controlled trials, nonrandomized controlled trials, and observational studies were included if the effects of exercise intervention in patients with BC before cardiotoxicity were examined.

Results: 10 studies were finally included. Physical exercise exerted some positive effects on systolic and diastolic function, biomarkers, hemodynamics and exercise capacity. The meta-analysis had a sample size of 193 participants, and the random effects model of 5 studies indicated that therapeutic exercise in BC patients who had not completed treatment may have positive effects by maintaining or improving left ventricular ejection fraction (LVEF). The mean difference between groups was .78 (-.22; 1.78), but this difference was not statistically significant.

Conclusions: Therapeutic exercise is a potential tool for the management of cancer treatment-induced cardiotoxicity, as it mitigates some of the cardiovascular side effects of medical treatment; however, there is limited evidence. The best parameters for the prescription of a dose of therapeutic exercise have yet to be clarified. LVEF needs to be complemented with other sensitive measures. More studies are needed to improve the quality of the evidence and to fully understand the role of therapeutic exercise in preventing/mitigating cardiotoxicity in women with BC.

BACKGROUND

Breast cancer (BC) and cardiovascular disease (CVD) are the main causes of mortality in women[1, 2], and share well-known risk factors[3] that have different complex physiological mechanisms. Moreover, patients with BC who undergo oncology therapies may experience cardiac dysfunction or cardiotoxicity[3], which is considered the most important acute and long-term side effect of these treatments[4]. This can be transitory[5] or permanent[6], and may result in the cessation of treatment[7], physical incapacitation[8] or increased risks of morbidity and mortality[9]. In fact, CVD has become one of the most significant causes of death in patients with BC, exceeding death caused by cancer[9, 10]: accounting for a 35% rate of mortality in BC survivors[11] and as a noncancer cause. Due to the risk of patients with BC developing CVD [12], the overall survival of these patients can be critically compromised.

Cardiotoxicity might affect the entire CV system, ranging from normal to severe myocardial damage or dysfunction[13], and it is mostly identified by a decrease in the left ventricular (LV) ejection fraction (LVEF)[14]. Current published guidelines recommend measuring it to identify the risk of possible CV complications[5, 8]. The gold standard method is cardiac magnetic resonance (CMR) imaging [15]; however, 3-D echocardiography is more cost-effective and has higher accuracy and reproducibility than 2-D echocardiography, which is the usually chosen due to its higher availability. Therefore, the assessment of LVEF is recommended before and during high-risk cardiotoxic agents[8], because an early decline during anticancer treatment can predict cardiotoxicity development[16], and will facilitate a more personalized intervention. Other methods such as global longitudinal strain (GLS), cardiac biomarkers, and electrocardiogram (ECG) are also recommended to complement the assessment[17]. Current research and clinical care are examining preventive solutions to decrease cancer treatment-induced cardiotoxicity[18], but scientific evidence is still very limited[19, 20].

Therapeutic exercise is currently perceived as an effective tool to address CV disorders throughout and beyond cancer treatments[21] and has already been declared as a potential cardioprotective strategy[22]. Currently, the research is focusing on the possible potential effects of therapeutic exercise on preventing or mitigating cardiotoxicity; however, while its effects are promising in this population[23], a recent roundtable established that it is still insufficient[24], and due to heterogeneous parameters of therapeutic exercise interventions, the optimal dose of exercise

remains unclear[25]. Nevertheless, there is a growing interest in this topic supported by ongoing studies[26–31].

Therefore, this study aims to identify the effects of therapeutic exercise and the optimal dose for interventions in cardio-oncology to minimize cancer treatment-induced cardiotoxicity in women with BC.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[32] was followed and the protocol was registered prospectively in the PROSPERO International Prospective Register of Systematic Reviews (Registration No. CRD42020155143, 20th May 2020).

Eligibility criteria

Studies that met the criteria are shown in Table 1 and a PICO strategy was used to retrieve relevant papers: Population: women with BC; Intervention: aerobic, resistance exercise or a combination of both; Comparison: studies with or without a comparative group; and Outcome: cardiotoxicity. In an initial title and abstract screening were excluded: reviews, protocols, guidelines, books, case studies, animal studies articles, had no exercise exposure, or irrelevant papers. In the full-text screening, records were excluded if they included other types of cancer in addition to BC, did not include LVEF as a variable, or if patients already ended their treatment.

Information sources and search strategy

The databases used were: MEDLINE (via PubMed), Web of Science, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Library. The search was conducted with MeSH terms and keywords. No restrictions on publication date were imposed, and no other additional filters were used. The last search was conducted on 30th August 2020. Databases were accessed via The University of Granada, Spain. Additionally, the reference lists of included articles were searched to identify additional studies. The search terms used in PubMed are shown in Supplementary table 1. The search terms were agreed upon by all authors and were modified to fit each database.

Study selection

The results were entered in Mendeley (Version 1.13.8, Windows, Elsevier) to remove duplicates. To determine eligibility, titles and abstracts were scanned by the independent reviewers using a template of Microsoft Office Excel 2019 (Version 2019 Windows, Microsoft Corporation).

Thereupon, full-text studies were reviewed for inclusion. Reasons for exclusion were recorded. Differences between reviewers were resolved by discussion, and a third reviewer was consulted if necessary.

Sensitivity and precision for the selected databases

This analysis was performed to determine the quality of databases.

Data extraction

The following data was collected: study characteristics (authors, year of publication, sample size), study population (cancer stage) and comparison group, design of the study, cardiac outcomes, details of time points of measurement, parameters of exercise intervention, controlled CVD or CV risk factors and main results (Table 2). Additionally, the parameters of the therapeutic exercise intervention or exposure (total duration of the program, frequency of sessions, intensity and duration of the session, type of exercise, and moment of exposure) are further detailed in Supplementary table 2. The overall number of sessions and the total training hours per participant were calculated in each study. Together, total training sessions and training time per participant and adherence of the participants are shown in Supplementary table 3. A descriptive analysis was

performed to extract conclusions about the benefits of different physical exercise doses.

Risk of bias

The risk of bias was assessed by two independent reviewers. The different types of studies were assessed independently: The Risk of Bias tool (RoB) 2.0 [33] was used to assess studies with an RCT design, and the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I)[34] was used to assess nonrandomized and observational studies. Interrater agreement was assessed by the kappa statistic index (values of .4 or less, from .4 to .75 and over .75 indicate poor, fair or excellent agreement, respectively)[35]. The scores of the two reviewers were compared, and differences were resolved by discussion. If no agreement was reached, a third reviewer was consulted. Study quality was rated on a scale of low to high risk of bias on the ROB 2.0 scale and from low to critical bias on the ROBINS-I scale. Quality assessments were also used to grade the strength of evidence of the data collected. Studies did not have to reach a determined score to be included in the review.

Data analysis

Random effects meta-analytic procedures were performed using STATA (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) for the

primary outcome: LVEF. Given the methodological design of the studies included in the systematic review, five studies were included in the meta-analysis of LVEF [36–40]; which assessed the cumulative effect of physical exercise on cardiotoxicity. Continuous data were extracted; given the variance in follow-up time points and in the lengths of treatment, we decided to include pretest and posttest means and SDs to compare groups. The standard deviation was calculated via Cochrane best practices if the data were not presented directly[41]. A standardized mean difference (Cohen d) and size effect (SE) were calculated for each study. The weighting was performed according to the degree of precision of the study. Finally, the overall effect size estimator for all studies was calculated. Heterogeneity between studies was studied statistically by means of the χ^2 test and quantified by means of the I^2 index[42].

RESULTS

Search results

In the initial search, 433 potential articles were identified. After excluding duplicates and those not meeting the inclusion criteria, 30 studies remained. After the full-text screening, one study was added from the manual search of the reference lists. In the end, 10 studies were finally included in this systematic review. The selection process is shown in Figure 1. The use of a therapeutic exercise program or exposure as prevention or mitigation of toxicity was assessed in all studies.

Sensitivity, precision, number needed to read and unique hits

The results for the sensitivity, precision, number needed to read (NNR) and unique hits are summarized in Supplementary table 4.

Participants, study characteristics, outcomes and design

The studies included 947 participants (165 in the intervention or exposure group and 124 in the comparison group in the experimental studies, and 658 in the observational studies). The sample from the experimental studies ranged from 17 to 70 patients and from 55 to 603 in the observational studies. The mean age of the participants in the therapeutic exercise program was 48.95 ± 8.87 years and 49.70 ± 9.21 years in the comparison groups and 50 ± 2.84 in the observational studies. All participants were women.

Concerning the comparison group, therapeutic exercise was compared to usual care[36, 37, 39, 40, 43, 44]; therapeutic exercise had no comparison group[6]; and physically active participants were compared to not physically active

participants[45]. The included studies were published from 2009 to 2020. Among the studies, four were RCTs[38, 40, 43, 44] (one was a proof-of-concept RCT[44]), two were prospective nonrandomized controlled trials[36, 39], one was a longitudinal nonrandomized controlled trial[37], one was a single-arm pre-post study[6], and two were observational studies[45, 46]. Participants, study main characteristics and cardiac outcomes are gathered in Table 2. The intervention details are shown in Supplementary table 2.

Risk of bias of the studies

The summary of the assessment of risk of bias is shown in Figure 2 and Table 3. The interrater agreement was excellent, with a kappa index of 0.77, between the two independent assessors. An agreement of 100% was reached through discussion. The majority of the RCTs presented methodological issues, especially deviations from intended interventions (75%), and the overall risk of bias was high (75%). In non-RCTs, the most common methodological issue was bias due to confounding with a moderate (66.67%) to a serious level of risk of bias (33.33%); 16.67% of the studies had a critical level of risk, 33.33% had a serious level of risk, and 50% had a moderate level of risk of bias.

Therapeutic exercise intervention

The therapeutic exercise intervention or exposure characteristics was described in terms of frequency, intensity, time, type, volume and progression in Supplementary table 2. The number of training sessions per participant (study total duration*sessions per week*adherence rates) was calculated from each study. The total training hours per participant were also calculated as the number of training sessions multiplied by the duration of each session (Supplementary table 3).

Acute effects of therapeutic exercise on cardiotoxicity

Considering the acute effects of exercise, Kirkham et al.[44] found a small but significant increase in LVEF (p=.02), an increase in systolic strain rate (p=.01), a decrease in systemic vascular resistance (SVR) (p=.01), and mitigation of NT-proBNP release (p=.01) in the intervention group compared to the usual care group[44]. On the other hand, the same research group later conducted another study[43] and found that performing the same therapeutic exercise session before each chemotherapy session (1 session every 2-3 weeks with a total of 4 sessions) had no significant effect on LVEF, longitudinal strain, twist, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) or cardiac troponin T (cTnT) release but had

general positive effects on hemodynamics, increasing cardiac output and resting heart rate and decreasing SVR (p=.01).

Cumulative effects of therapeutic exercise on cardiotoxicity

Regarding the cumulative effects of therapeutic exercise, observational studies were separated from the rest of the studies included, and the results are summarized in Table 2.

On the one hand, studies found that physical exercise increased LVEF (p<.05)[40] or maintained LVEF (p=.003)[38], maintained the ratio of early diastolic inflow to late diastolic inflow (E/A), prolonged the isovolumic relaxation time (IVRT), and prevented an increase in NT-proBNP[40]. The cardiac troponin I (cTnI) was increased but was lower in the therapeutic exercise group (p=0.1)[36]. Physical exercise also improved hemodynamics[46] and improved, maintained or prevented a decline in exercise capacity[6, 36, 38–40].

On the other hand, other studies found no effect of physical exercise on improving or maintaining cardiac function[6, 36, 39, 47], and troponin I increased over 4 months and remained elevated at 12 months[37] despite the use of physical exercise.

Regarding the observational studies, Upshaw et al.[46] reported that higher physical activity levels before treatment were modestly associated with an attenuation of the decrease in LVEF. Nagy et al.[45] reported a prevention in diastolic dysfunction one year after treatment (p<0.05), and heart failure events were more frequent in the less active group than in the nonactive group (19.45% in the physically active group compared to 68.42% in the physically nonactive group)[45].

Cardiovascular disease and risk factors

In general, both experimental and observational studies included patients without CVD/risk factors and/or CV risk was well controlled[43–45]. The experimental studies registered the cases of hypertension [(n=18)[40], (n=8)[38], (n=3)[39], (n=2)[43, 44], (n=1)[36, 37], [antihypertensive medication (n=3)[6]], diabetes [(n=7)[40], (n=1)[6, 38, 39, 43, 44]], dyslipidemia (n=6)[38], (n=2)[36, 37] [cholesterol lowering medication (n=1)[6]], smoking status [smoker (n=3)[6] and former smoker (n=8)[38], (n=4)[6]] or angina (n=1)[43, 44] or previous heart failure (n=1)[38]. In one of the observational studies, 35% of patients reported current/previous tobacco use, 30% reported hypertension, 24% reported hyperlipidemia, and 9% reported diabetes[46]; in the other observational

study, the patients had no CV risk factors[45].

Adherence

In the experimental studies, the adherence was 59%[6], 63%[39], 76%[36, 37], 98.7%[38] or 100%[43, 44] or not reported[40].

Adverse events

Most studies reported interventions to be safe and reported no adverse effects.

Meta-analysis

Regarding the outcome variable LVEF, an exploratory analysis was conducted with some of the studies[36–40] included in this systematic review, with a joint sample of 193 participants. The full results are summarized in Figure 3. No significant association between groups was found (d=0.78; 95% CI, -0.22, 1.78); p=0.13; I2=89.41%), although clinically positive results were observed in favor of the intervention.

DISCUSSION

Based on current knowledge, we suggest that therapeutic exercise may be cardioprotective with acute and cumulative effects, especially when physical exercise is performed before cardiotoxicity is established. The results of the meta-

analysis present positive effects regarding the mitigation of cancer treatment-induced cardiotoxicity. These findings support he conclusion of a recent consensus of experts[23], who identified therapeutic exercise as a promising tool. Moreover, the present review clarifies the effects of therapeutic exercise in humans. Moreover, this study analyses the most effective parameters for an adequate dose of therapeutic exercise and reveals that the combination of many assessments is the key to the proper detection and treatment of cardiotoxicity. Nevertheless, there are still few studies in this field and many ongoing trials with no results yet[26–31]; thus, the evidence looks promising, but it is still insufficient.

Effect of therapeutic exercise

The cardioprotective effects of therapeutic exercise have been shown, including the improvement or maintenance of LVEF[38, 40, 44] and benefits for diastolic function (E/A [40, 45], IVRT[40], deceleration time (DT) interval[40]), biomarkers (NT-proBNP release[40, 44], cTnI release[36]), hemodynamics (resting heart rate, SVR and cardiac output[43]), and exercise capacity (maximal oxygen uptake (VO2max) and Vo2max/kg[40], peak oxygen uptake (VO2peak) and peak power[36] and maintaining 6-minute walking test (6MWT) distance to major walk capacity[38]). In

addition, it should be noted that these effects occur when women participate in an exercise program after being diagnosed with cancer as well as when women who were active before diagnosis had a later cardiac decline and less frequent heart failure (HF) events participate in an exercise program[45].

Supervised moderate-to-vigorous aerobic exercise was most commonly used in the included studies; however, there was still heterogeneity between the parameters of the exercise (program duration, frequency and volume of sessions) that made it difficult to define a common dose to benefit all outcomes. Additionally, the studies reported no adverse effects[6, 36, 37, 43, 44] and good adherence (above 76%, with the exception of one article, which had an adherence of 59%[6]), which reinforces the idea that physical exercise exposure is safe and feasible.

The meta-analysis suggests that women with BC who participate in therapeutic exercise during treatment improve or maintain LVEF as opposed to the comparison group. Two of the studies started when patients could already be at risk of cardiotoxicity[6, 38]. Despite the conflicting results, it seems that it is better to perform a program before cardiotoxicity settles[40] and even to stay active before diagnosis[48]. The high heterogeneity of the

meta-analysis may be due to the limited number of high-quality studies available, the different design of the trials, the clinical heterogeneity among the interventions (different prescriptions regarding duration and volume) and the risk of bias of the trials. Therefore, the results must be interpreted with caution.

Acute effects of therapeutic exercise

One single bout[44] of 30-min vigorous aerobic exercise 24 h before the doxorubicin sessions had positive effects on LV function, cardiac biomarkers and hemodynamics. However, these improvements are not maintained over time[43], although they do produce other systemic benefits (e.g., in cardiac output and HR) when the same protocol is repeated before each chemotherapy session. These authors[43] claim that the hypotheses that worked in rats was not fulfilled[49, 50] maybe because the protocol was not optimal for such improvements in humans. As authors point out, participants received a lower dose of therapeutic exercise compared to the animal models, and participants had cardioprotection due to low baseline blood pressure. This could indicate that rats are not an optimal model for CV research[51] and that a lower blood pressure reduces the risk of CVD events[52]. The acute cardioprotective effects can be due to immediate beneficial effects on

cardiotoxicity, as the authors discuss, conferred by therapeutic exercise: nitric oxide, vasodilation, antioxidants or the metabolism or pharmacokinetics of doxorubicin. This finding is in concordance with other authors who found better chemotherapy assimilation with therapeutic exercise[53–56].

Cumulative effects of therapeutic exercise

Effects on cardiac function

The results are conflicting regarding moderate-high intensities, showing that high volumes at that intensity are needed (>34 h) to achieve positive effects on systolic[38–40] and diastolic[45] function, both before[45, 46] and during anticancer treatment[38, 40]. These results are in line with compelling evidence that claims that at least moderate-high volumes and intensities are needed to decrease the risk of chronic diseases and risk of death[57, 58], possibly by avoiding sedentarism having a positive effect on cardio-metabolic risk factors[59], lowering blood pressure, rising insulin sensitivity, and having a more favorable plasma lipoprotein profile[60] and major CV effects in the heart, blood vessels and blood stream[60].

Studies that did not find positive results had no objective markers to control intensity and imprecise periodization and unsupervised sessions[36, 37], low adherence[6] and a low volume intervention (<25 h)[6, 36, 37, 39].

Effect on cardiac biomarkers

The results are not consistent, as the majority of studies had no differences between groups. When benefits were found, only some biomarkers for cardiac damage (cTnI[36] and NT-proBNP[40]) were identified. With these results, we can claim that biomarkers alone may not be the only method to assess cardiotoxicity, so there is the need to compliment with other assessments. It is suggested that they need to be assessed in a more sensitive way, e.g., 24 h close to the chemotherapy session, where an increase in the troponin level, followed by a less marked increase in 24 h, is a hallmark of necrosis[61].

Effects on exercise capacity

The results related to exercise capacity are more consistent, showing improvements[6, 40] or preservation[36, 38, 39] in Vo2max[40][6], Vo2peak[6, 36, 39] and 6MWT distance[38]. Given the prediction of VO2peak of chemotherapy-induced left ventricular dysfunction[62], the relation of these variables to cardiopulmonary function[36, 37], and the inverse relationship of peak exercise capacity to an increase in HF risk and HF mortality[63, 64], the observed benefits are relevant. This

variable is so valuable that it is considered a "vital sign", predicts CV mortality[65] and may be considered another essential marker of cardiac function when at risk of cardiotoxicity[66]. It is important to note that in the study by Haykowsky et al.[6] adherence played an important role, as benefits were found in patients with >55% adherence and in the study by Kirkham et al. [39] in which participants with high adherence had almost significant attenuation, while in the low adherence group, there was a significant reduction.[39] The preservation in the study by Howden et al.[36] was lost in the follow-up[37] as the authors discussed may be due to the lack of physical activity in their participants, which is in line with other studies that have suggested that the lack of adherence may result in significantly fewer VO2peak benefits[67].

Assessment of cardiotoxicity

Measuring LVEF should always be considered when the risk of cardiotoxicity is present and, if possible, should be completed with the assessment of longitudinal strain or supplemented with other markers, such as cardiac function measurements, circulating biomarkers[68] or exercise capacity[66], to detect cardiotoxicity as early as possible. The use of appropriate diagnostic methods is essential because early detection and

intervention would guarantee better cardiac function recovery[69]. In this sense, the lack of use of these complementary measures or even the use of inadequate protocols in the analyzed studies may be behind the lack of conclusive findings regarding possible exercise-induced improvements.

Sensitivity and precision of the databases

The highest sensitivity was recorded articles from the Web of Science databases, indicating that this database had the lowest probability of missing papers relevant to the search. This study also found a low precision of databases for this topic except for Cochrane, showing that databases retrieved too many irrelevant papers. CINAHL was the most ineffective database for this topic due to the lack of sensitivity and precision. This database is more specialized in the nursing field, which can explain these results. Given that CINAHL did not retrieve any relevant hit and due to the added effort that demands to adapt the search strategy, researchers might reconsider using the CINAHL databases in future searches related to therapeutic exercise in patients with BC[70].

Strengths and limitations

This review has some strengths and limitations. The strengths were as follows:

we covered a wide range of databases to retrieve articles; there was a wide period of time covered in the review, from 2009 to 2020; we used the PRISMA 2009 checklist to report the systematic review[32]; we assessed the risk of bias; we included a sensitivity/precision analysis that may help when conducting similar search strategies; participants had homogeneous characteristics (early stage of BC (I-II/I-III), and CVD or CV risk factors); and we extracted data to perform a meta-analysis. The limitations were as follows: we could not draw quantitative conclusions because of high levels of study heterogeneity; only 5 studies were included in the quantitative analysis, and most of the studies had small samples and thus may not have had enough power; there were only 4 RTCs included in the review; the review focuses solely on patients with BC; there was a high risk of bias in most of the studies; and the heterogeneity of the parameters of interventions between studies prevented the selection of a single optimal dose of exercise.

Conclusion

This systematic review revealed that therapeutic exercise may have potential in the management of cardiotoxicity and that is may mitigate some of the CV side effects of medical treatment. Its acute effects appear to be positive for cardiac function or

to be more systemic instead of targeted to cardiac benefits, and if the exercise if performed over long periods of time, the cumulative effects could help to mitigate some aspects of cardiotoxicity. However, the benefits are unclear. Therapeutic exercise has been shown to be safe and feasible; however, the limited studies available and the heterogeneity among the existing interventions suggest that more high-quality research is necessary. The best parameters for the prescription of therapeutic exercise dose have yet to be clarified. More high-quality studies, especially randomized controlled trials, are needed. Additionally, although LVEF is widely used, the additional use of other more sensitive measures, such as left ventricular longitudinal strain, cardiac biomarkers and exercise capacity, would be useful.

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Conflict of interest

The authors declare no conflict of interest

Available of data and material

All data generated or analyzed during this study are included in this published article

Code availability

Not applicable

Author's contributions

Conception or design of the work: ICV, NGL, RPB. Data analysis: PPM, MLL, AGS, MLG. Drafting the article: PPM, NGC, MLL, ICV. Final approval of the revision to be published: PPM, NGC, AGS, MLG, RFB, ICV.

Consent for publication

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70.   Beckles Z, Glover S, Ashe J, et al (2013) Searching CINAHL did not add value to clinical questions posed in NICE guidelines. J Clin Epidemiol 66:1051–1057. https://doi.org/10.1016/j.jclinepi.2013.04.009

Identification

Records identified through database searching
(n = 433)

Screening

Records after duplicates removed
(n = 310)

Records screened
(n = 310)

Records excluded (title/abstract screening
(n = 280)

Reviews: 67
Protocols: 12
No exercise exposure: 46
Guideline: 3
Book: 5
Case studies: 5
Rats: 19
Not relevant: 123

Eligibility

Full-text articles assessed for eligibility
(n =30)

Records identified through hand-search (n = 1)

Full-text articles excluded
(n = 20)

Book: 1
Review: 6
Does not include LVEF: 3
No exercise exposure: 2
Patients ended treatment: 2
Animals: 1
Special Issue: 2
Included other cancer types: 1
Case studies: 2

Included

Studies included in the systematic review
(n =10)

Figure 1. Diagram flow.

Figure 2. Assessment of the risk of bias scale risk of bias assessment of RTCs.
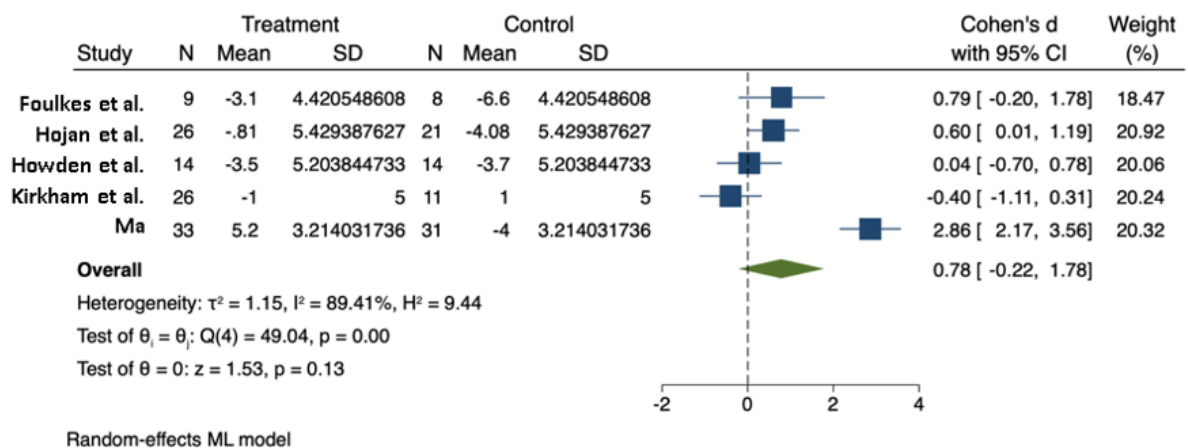
Figure 3. Results of a preliminary meta-analysis for the LVEF.

Table 1. Inclusion and exclusion criteria.	
Inclusion criteria	
Patients	Women (>18 years) Diagnosed with BC at any stage.
Intervention	Any type of physical exercise or activities orientated to achieve health benefits[93] or any exposure to sport activities.
Comparator	No restriction was applied.
Outcomes	Includes LVEF as a measure of cardiac function regarding cardiotoxicity.
Study design and characteristics	RTCs Non-randomized trials. Quasi-experimental Observational studies.
Language	English or Spanish
Exclusion criteria	
-Reviews, guidelines, opinions, editorials, commentaries, letters, conference abstracts, case-control and case series studies. -Patients with other types of cancer. -Studies that included patients who finished treatment. -Studies in animals.	
BC, breast cancer; LVEF, left ventricular ejection fraction, RCT, randomized controlled trials.	

Table 2 Characteristics of studies regarding therapeutic exercise for cardiotoxicity.

Author/ Year publication	Participants/ Comparison or control group	Cardiac outcomes	Measured time points	Controlled CVD, or CV risk factors	Adverse effects	Main results
RCT studies						
Hojan et al., 2020	- Women, HER2+, stage I-III BC (n=34) undergoing no more than 6 months of trastuzumab after chemotherapy or radiotherapy. - UC (n=34).	Cardiac function: - LVEF, GLS, LAVI, RVEF, TAPSE, E/A. Biomarkers: - MYO, IL-6, ALT, AST, CK, CK-MB. Hemodynamics: - HR, blood pressure. Exercise capacity: - 6MWT distance.	Previous to the start of the intervention (minimum 3 months transtuzumab). After the intervention (9 weeks).	Yes	Not reported	No significant changes in LVEF in the intervention group, compared to the decrease in UC group (p<.05). No significant difference in blood parameters (p<.05). No changes in 6MWT in the intervention group compared to the decrease in the UC group (p>0.05).
Kirkam et al., 2017	IG: Women, stage I-III BC, scheduled anthracycline (doxorubicin) chemotherapy (n=13). - UC (n=11).	Cardiac function: - LVEF, longitudinal strain, cardiac output, LV volumes, stroke volume, E/A ratio, systolic and diastolic SR, twist, twist velocity and untwist velocity. Biomarkers: - NT-proBNP, cTnI, Hb. Hemodynamics: HR, blood pressure, pulse pressure, mean arterial blood pressure, SVR.	0-14 days before the first doxorubicin session (baseline). 24-48 h after the first doxorubicin session (acute follow-up).	Yes	Reported (None)	One single session of therapeutic exercise performed 24 h before the first doxorubicin session, increased LVEF (p=.02), maintained strain, cardiac output, stroke volume, E/A ratio, end-diastolic, diastolic strain rate, twist and untwist velocity (all p=.01); attenuated NT-proBNP release (p<.01), and decreased SVR (p=.01)
Kirkham et al., 2018	- Women, stage I-III BC, undergoing anthracycline (doxorubicin) chemotherapy (n=13). - UC (n=11).	Cardiac function: - LVEF, longitudinal strain, cardiac output, LV volumes, stroke volume, E/A ratio, twist, LV mass. Biomarkers: - NT-proBNP, cTnI, Hb. Hemodynamics: - HR, blood pressure, mean arterial blood pressure, SVR.	0-14 days before the first doxorubicin session. 7-14 days after the last doxorubicin session.	Yes	Reported (None)	Effect of the intervention improving cardiac output, systemic vascular resistance, mean arterial pressure, resting HR (p=.01). No effect on longitudinal strain, twist or cardiac biomarkers.
Ma, 2018	- Women with BC undergoing anthracycline chemotherapy (n=35). - UC (n=35).	Cardiac function: - LVEF, E/A, DT, IVRT interval. Biomarkers: - NT-proBNP, cTnI, Hb, SCr, CK-MB. Exercise capacity: - VO2max/kg, VO2max, VO2maxHR, HRmax.	Previous to the start of anthracycline chemotherapy. 6 months after chemotherapy. 12 months after chemotherapy.	Yes	Not reported	The intervention Increased LVEF and prolong IVRT, compared to the control group where LVEF, DT interval and E/A decreased (p<.05). The intervention also maintained levels of biomarkers while increased in the UC (p<.05), increased VO2max/kg and VO2max.
Non-RCT studies						
Foulkes et al., 2019	- Women that had stage I-III BC, underwent anthracycline chemotherapy (n=14). - UC (n=14)	Cardiac function - LVEF, GLS, LV volume, LAVI E/A, E e', DT, LV mass index. Biomarkers - BNP, cTnI, Hb. Exercise capacity: VO2 peak, peak HR, power output, respiratory exchange ratio, arterio-venous O2 difference, peak cardiac output, peak stroke volume.	Baseline (pre anthracycline). 4 months follow-up 16 months follow-up	Yes.	Reported (None)	Despite the intervention, LVEF decreased, GLS decreased, cTnI increased. VO2peak was higher during the study in the IG (p=.015), but the group-time interaction was not significant (p=.1).
Howden et al., 2019	- Women with stage I-III BC, undergoing anthracycline chemotherapy (n=14). - UC (n=14)	Cardiac function: - LVEF, GLS, cardiac output, LV volumes, peak stroke volume, E/A, E e', DT, LAVI, LV mass. Biomarkers - BNP, cTnI, Hb. Exercise capacity - VO2peak, HR peak, power output, respiratory exchange ratio, arterio-venous O2 difference, peak cardiac output.	Pre anthracycline treatment 3 wk after completing anthracycline treatment	Yes	Reported (None)	With the intervention, LVEF had small reduction in both groups (p=.003). cTnI rose in both groups (p<.001), but was lower in the exercise group. There was a VO2peak (p=.01) and peak power preservation (p=.013).

Author/ Year publication	Participants/ - Comparison or control group	Cardiac outcomes	Measured time points	Controlled CTD, or CV risk factors	Adverse effects	Main results
Kirkham et al. 2020	- Women that had stage I-III BC undergoing anthracycline chemotherapy (doxorubicin and cyclophosphamide) (n=26) - UC (n=11)	Cardiac function - LVEF, longitudinal strain, longitudinal strain rates, E/A ratio. Hemodynamics - HR, blood pressure, cardiac output, stroke volume, SVR. H	0-14 days prior to the first anthracycline treatment. 7-14 days after the last anthracycline treatment.	Yes	Not reported	The intervention had no effect on LVEF, longitudinal strain strain rates, and E/A. It had effects on cardiac output (p=.03) and SVR. (p=.01) between groups.
Cuasi-experimental single arm pre-post study						
Harkivskyv et al. 2009	- Women with HER2-positive I-III stage BC (n=17), with a combination of: a) fluorouracil, epirubicin and cyclophosphamide OR doxorubicin and cyclophosphamide followed by trastuzumab (n=3). b) anthracyclines (as "a" option) followed by docetaxel and trastuzumab (n=6). c) doxetaxel with carboplatin with trastuzumab (n=8).	Cardiac function: - Rest and peak LVEF, LV volumes, LV mass. Biomarkers: Hb. Hemodynamics - blood pressure Exercise capacity: - Vo2max, VO2peak, HRpeak; power output, respiratory exchange ratio.	Before trastuzumab After 4 months since the start of trastuzumab.	Yes	Reported (None)	Despite the intervention, LVEF decreased. Resting LV volumes increased. Improvements in VO2peak only when participants attended ≥55% of the sessions.
Observational studies						
Nagy et al., 2016	- Women operated of right-sided I-IIBC, that underwent anthracycline (doxorubicin or epirubicin) chemotherapy: - physically active (PA) (n=36) - non physically active (NPA) (n=19)	Cardiac function: - LVEF, E/A ratio, DT, mitral inflow (mitral E velocity; mitral A velocity), pulmonaric venous S and D, S/D ratio. TDI parameters (Ea/Aa septal, posterior, septal', inferior, lateral, anterior, septE). Hemodynamics - HR, blood pressure Symptoms - Heart failure (dyspnea, reduced physical capacity; fatigue, foot swelling, night-time urination).	Before the first chemotherapy treatment. In the middle of anthracycline therapy. 1-year after the first chemotherapy. 2-years after the first chemotherapy. 5-years after the first chemotherapy (via telephone)	Yes	Not reported	Parameters that decreased later in time in the PA group: E/A, Ea/Aa ratio in the septal segment, and later in all TDI parameters (p<.05). Symptoms of heart failure had higher incidence in the PNA group.
Upshaw et al., 2020	- Women with BC stage I-III) and IV (1.5%) treated with doxorubicin and/or trastuzumab (n=603) with a combination of: a) doxorubicin with cyclophosphamide and paclitaxel (n=362). b) trastuzumab with decetaxel and cyclophosphamide or carboplatin (n=157). c) doxorubicin with cyclophosphamide and trastuzumab and paclitaxel (n=84).	Cardiac function: - LVEF, longitudinal strain, E/e' and diastolic function grade.	Baseline: after diagnosis but before initiation of treatment. Periodically depending on the group of treatment. At 24 and 36 months in every group.	Yes	Not reported	Modest associations of physical activity with attenuation in the decline of left ventricular ejection fraction (p=.02)

	D1	D2	D3	D4	D5	D6	D7	Overall judgement
Foulkes et al.	Moderate	Low	Low	Low	Moderate	Low	Moderate	Moderate
Haykowsky et al.	Serious	Low	Serious	Low	Serious	Moderate	Low	Serious
Howden et al.	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Kirkham et al.	Moderate	Low	Serious	Low	Low	Low	Moderate	Serious
Nagy et al.	Serious	Critical	Moderate	Low	Low	Moderate	Moderate	Critical
Upshaw et al.	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

Table 3. Robins-I scale for the risk of bias assessment of non-randomized studies.

Domains. D1: Bias due to confounding. D2: Bias in the selection of participants into the study. D3: Bias in the classification of interventions. D4: Bias due to deviations from intended. D5: Bias due to missing data. D6: Bias in the measurement of outcomes. D7: Bias in selection of the reported results.

106

	Concept	Terms
		Supplementary table 1. Terms that composes the search strategy for PubMed.
	Concept	Terms
#1	Intervention	(exercise[MeSH Terms] OR exercis*[tiab] OR physical activit*[tiab] OR physical exercis*[tiab] OR acute exercis*[tiab] OR isometric exercis*[tiab] OR aerobic exercis*[tiab] OR exercis* training[tiab] OR resistance training[MeSH Terms] OR resistance training[tiab] OR strength* training[tiab] OR weight-lifting strength*[tiab] OR weight-lifting exercis* program[tiab] OR weight-bear* strength* program[tiab] OR weight bear* exercis* program[tiab] OR weight bear* exercis* program[tiab] OR exercise therapy[MeSH Terms] OR exercis* therap*[tiab] OR remedial exercis*[tiab] OR rehabilitation exercis*[tiab] OR aquatic exercis*[tiab] OR aquatic physiotherapy[tiab] OR aquatic therapy[tiab] OR aquatic physical therapy[tiab])
#2	Condition	(breast neoplasms[MeSH Terms] OR breast neoplasm* [tiab] OR breast cancer[tiab] OR breast tumor[tiab] OR breast cancer[tiab] OR mammary cancer[tiab] OR malignant neoplasm* of breast[tiab] OR breast malignant neoplasm*[tiab] OR breast malignant tumor*[tiab] OR malignant tumor of breast[tiab] OR cancer of breast[tiab] OR cancer of the breast[tiab] OR mammary carcinoma*[tiab] OR mammary neoplasm*[tiab] OR breast carcinoma*[tiab])
#3	Outcome	(cardiotoxicity[MeSH Terms] OR cardiotoxicit*[tiab] OR cardiac toxicit*[tiab])
#1 AND #2 AND #3		

Supplementary table 2. Studies' parameters of therapeutic exercise intervention or exposure detailed.

Study	Group	Program duration	Frequency Sessions/wk	Intensity	Time, volume Warm-up (Min)	Session (min)	CD (min)	Exercise and sessions type	Progression	Moment
Howden et al.	Intervention (n=14) UC (n=14)	12 wk or 8 wk (if they receive a chemotherapy dose-dense protocol)	3 sessions/wk (2 supervised and 1 home-based)	Moderate-vigorous (supervised) Moderate (home-based) Resistance not defined	NS	30 aerobic + 30 resistance (supervised); 30-60 aerobic (home-based)	NS	Aerobic, resistance, combined (supervised and unsupervised)	Periodized, 2-10% increases (non-treatment week)/decreases (treatment week)	After the first session of chemotherapy, until the end of it.
Kirkham et al.	Intervention (n=26) UC (n=11)	8-12 wk	3 sessions/wk	Moderate-vigorous, 50-75% HRR	NS	20-30 aerobic + resistance (NS)	NS	Aerobic, resistance; supervised	Periodized, progressions every 1-2 weeks as tolerated	During chemotherapy
Ma	Intervention (n=35) UC (n=35)	16 wk	3 sessions/wk	Vigorous intensity, HIIT, 60-70% / 90-95% HRmax (HIIT).	10	5 vigorous*3 moderate interval (30 in total).	10	Aerobic, Stretching; supervised	Each bout same characteristics	From the first session of chemotherapy until the end.
Observational studies which specified the physical exercise exposure										
Nagy et al.	Physically active (n=36)	NS	≥4 sessions/wk	NS	NS	30	NS	Any individual or team sports; unsupervised.	NS	Before diagnosis
	Non physically active (n=19)	NS	<4 sessions/wk	NS						

CD, cool-down period; RCT: randomized clinical trial; wk: week; HIIT: high-intensity interval training; HRR, heart rate reserve; HRmax, maximal heart rate; HW, healthy women; NS, not specified; UC, usual care;

Supplementary table 3. Studies' total training sessions, training time, adverse events and adherence.

Study	Training sessions / participant	Total training time / participant	Adherence participants attendance	Training sessions and of participant	Total training time / participant	Adherence participants
	Intervention/exposure group			Comparison group		
Acute effects						
Kirkham et al.	1	0.75 h (45 min)	13/13; 100%		UC	11/11
Kirkham et al.	4	3 h	13/13; 100%		UC	11/11
Cumulative effects						
Foulkes et al.	18.3 (n=3); 27.4 (n=11).	16.8 h (n=3), 25.1 h (n=11)	9/14; 76%		UC	8/14
Haykowsky et al.	21.2	15.9 h	17/21; 59%	Does not have		
Hojan et al.	44.4	68.5 h	26/34; 98.7%		UC	21/34
Howden et al.	18.3 (n=3); 27.4 (n=11).	16.8 h (n=3), 25.1 h (n=11)	14/14; 76%		UC	14/14
Kirkham et al.	15.12 (8 wk) 22.68 (12 wk)	7.56 h (8 wk) 11.34 h (12 wk)	26/30 63%		UC	11/11
Ma	39.27	32.72 h	31/35 NS		UC	33/35

The total amount of training sessions per participant was calculated multiplying sessions per week*study duration*adherence rate (if specified); the not specified, was imputed as the mean of the adherence of the studies which was 81.81%.

Supplementary table 4. Sensitivity, precision, NNR and unique hits of the search.						
Databases	Total Hits Retrieved	Relevant hits retrieved	NNR	Unique hits	Sensitivity	Precision
Pubmed	53	7	8	0	70	13
Web of Science	201	9	22	1	90	4
Scopus	153	5	31	0	50	3
CINAHL	22	0	-	0	0	0
Cochrane	4	2	2	0	20	50
Hand search		1	1			
TOTAL	433					

The number of hits is the remaining after duplicates were 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 (%).

STUDY IV

ATTENUATING TREATMENT-RELATED CARDIOTOXICITY IN WOMEN RECENTLY DIAGNOSED WITH BREAST CANCER VIA A TAILORED THERAPEUTIC EXERCISE PROGRAM: PROTOCOL OF THE ATOPE TRIAL

Physical Therapy

2021

STUDY IV. ATTENUATING TREATMENT-RELATED CARDIOTOXICITY IN WOMEN RECENTLY DIAGNOSED WITH BREAST CANCER VIA A TAILORED THERAPEUTIC EXERCISE PROGRAM: PROTOCOL OF THE ATOPE TRIAL

ABSTRACT

Introduction: Therapeutic exercise is already used to ameliorate some of the side effects of cancer treatment. Recent studies examined its preventive potential regarding treatment-related toxicity, which can increase the risk of functional decline and lead to disease recurrence and death.

Objective: This trial will examine whether the ATOPE (Tailored Therapeutic Exercise and Recovery Strategies) program, performed before treatment (ATOPE-B), can mitigate the onset and extent of cardiotoxicity beyond that achieved when the program is followed during treatment (ATOPE-I) in recently diagnosed breast cancer patients.

Methods: The intervention has a preparatory phase plus 12-18 sessions of tailored, high-intensity exercise, and post-exercise recovery strategies. 58 women recently diagnosed with breast cancer, in risk of cardiotoxicity due to anticancer treatment awaiting surgery followed by chemotherapy and/or radiotherapy, will be randomised to either group. In a feasibility study, measurements related to recruitment rate, satisfaction with the program, adherence to them, the retention of participants, safety, and adverse effects will be explored. In the main trial, the efficacy of these interventions will be examined. The major outcome will be cardiotoxicity, assessed echocardiographically via the left ventricular ejection fraction. Other clinical, physical, anthropometric outcomes, biological and hormonal variables, will be also assessed after diagnosis, after treatment, 1 year after treatment ends, and 3 years after treatment ends.

Conclusion: Given its potential effect on patient survival, the mitigation of cardiotoxicity is a priority, and physiotherapists have an important role in this mitigation. If the ATOPE-B intervention returns better cardioprotection results, it may be recommendable that patients recently diagnosed, follow this program.

INTRODUCTION

Breast cancer (BC) outcomes are improving, even though the incidence of the disease is rising[1]. Advances in both early detection and medical treatment[2] have reduced mortality rates[3], but led to an increase in the number of BC survivors who suffer important short- and long-term problems induced by the treatment received[4] - problems that can leave survivors at risk of disease recurrence[5], of developing comorbidities[6], or of death[7–9]. Preventing or reducing the side effects of treatment is of great importance[10].

The surgical treatment of BC is commonly complemented by radiotherapy and/or systemic therapy such as hormonal therapy, targeted therapy or chemotherapy[11]. Unfortunately, these treatments, though necessary to combat the disease, can be very toxic and have a strong impact at the cardiovascular level[12,13]. Such cardiotoxicity is often caused by anthracyclines such as doxorubicin and epirubicin[14,15], but also by radiotherapy[15] and the use of targeted therapeutic agents[16,17]. The degree of cardiotoxicity caused by anthracyclines is dose-dependent, but increases when they are combined with radiotherapy[18,19] or with monoclonal antibodies against human epidermal growth factor receptor 2 (HER-2)[20]. The mechanisms of cardiotoxicity are yet to be fully explained, but anthracycline-induced toxicity is thought to affect cardiomyocytes and mitochondria[21], and radiation is thought to damage the cardiac vasculature[22]. Some of the alterations caused by cancer treatment appear to be mediated via the generation of reactive oxygen species (ROS) that then damage the cardiomyocytes[17].

Both short and long-term cardiotoxicity can cause structural and functional changes[13], reducing the efficacy of the cardiovascular system and diminishing left ventricular function[23]. The risk of a cardiovascular event increases in patients who have pre-existing cardiovascular disease (CVD)[24], cardiovascular risk factors[25,26], and older patients [26]. It is reported that death from cardiac causes exceeds that caused by cancer in > 5-year survivors of BC who are older than 66 years of age[24]. Indeed, women with BC are at a 1.9-times greater risk of death by CVD than those in the cancer-free population[27]. Besides, the appearance of cardiotoxicity during treatment may require that treatment be withdrawn[28]. It is therefore imperative that preventive and cardioprotective strategies be developed [29].

Therapeutic exercise programs can protect the cardiovascular system from cardiotoxicity both during and after cancer

114

treatment [30–32]. Recent clinical studies also demonstrated the potential of physical exercise programs to prevent and mitigate toxicity[33–35]. Therapeutic exercise performed 24 h before a doxorubicin treatment session has been associated with a reduced risk of acute heart failure, an increase in systolic function[36], better hemodynamics, improved mood, and reduced weight gain. However, no effects on subclinical cardiotoxicity have been noted[37]. Furthermore, it is known that physical exercise before surgery in patients with non-small cell lung cancer increases cardiorespiratory fitness, a predictor of survival[38].

However, a knowledge gap exists regarding the timing and dose of therapeutic exercise that may best mitigate cancer treatment-induced cardiotoxicity, and models that explain the benefits of therapeutic exercise in this respect are needed to provide the rationale for future clinical studies. Most studies involved moderate-intensity continuous cardiovascular exercise, but high-intensity training has started to receive more interest[39] and is safe and feasible for patients with cancer[40]. However, it is important to tailor (dose) the duration, type and intensity of exercise, and the exercise-recovery conditions, to the patient and his/her condition[41]. Patients with cancer may show significantly reduced heart rate variability (HRV)[42], the change in which

has been used to determine whether the body is responding to physical exercise[43].

The main aim of the trial will assess whether ATOPE-B (ATOPE before cancer treatment) mitigates the onset and extent of cardiotoxicity beyond that achieved by ATOPE-I (ATOPE in treatment), The secondary aim will be to evaluate the effects of the ATOPE program in clinical variables, survival outcome, physical, anthropometric/body composition and biological variables.

METHODS

The protocol adheres to the recommendations of the SPIRIT checklist and diagram[44,45] (Fig. 1). For the description of the intervention, the Template for Intervention Description and Replication (TIDieR) has been followed[46]. Table 1. Gathers the details of the ATOPE program.

Intervention

The ATOPE program is a 12-18 sessions-program along 6-8 weeks, depending on the treatment scheduled for each patient, supervised (one-on-one) program of therapeutic exercise that consists of multimodal therapeutic exercise (aerobic, strength, motor control exercises, myofascial techniques and breathing exercises), implemented by a

Study Period	Post-diagnosis			Before treatment	In treatment		End of treatment	
	Enrollment	Baseline	Allocation	ATOPE	ATOPE	Second assessment	1 year after	3 years after
TIMEPOINT	$-t_1$	t_0	0			t_1	t_2	t_3
ENROLLMENT:								
Eligibility screening	X							
Informed consent	X							
Program information	X							
Allocation			X					
INTERVENTIONS:								
ATOPE-B				●———————●				
ATOPE-I					●———————●			
FEASIBILITY OUTCOMES								
Recruitment rate	X							
Satisfaction with ATOPE				X	X			
Satisfaction with ATOPE+ app				X	X			
Adherence to ATOPE				X	X			
Retention		X	X	X	X	X	X	X
Safety and adverse effects				X	X			
Barriers and facilitators				X	X			
EFFICACY OUTCOMES								
PRIMARY OUTCOME								
Cardiotoxicity		X				X	X	X
SECONDARY OUTCOMES:								
Other cardiac outcomes		X				X	X	X
Cardiac autonomic nervous system function		X				X	X	X
Quality of life		X				X	X	X
Cancer treatment: halted or altered?					X	X	X	X
ATOPE: alterations?				X	X			
Survival		X				X	X	X
Cardiorespiratory fitness		X				X	X	X
Functional capacity		X				X	X	X
Strength		X				X	X	X
Flexibility		X				X	X	X
Waist and hip circumferences		X				X	X	X
Body composition		X				X	X	X
Muscle quantity and quality		X				X	X	X
Oxidative stress		X				X	X	X
Immune status		X				X	X	X
Systemic inflammation		X				X	X	X

Figure 1. Details of enrollment, interventions, and assessments according to the SPIRIT diagram.

Table 1. The ATOPE Program in Detail[a]

	Mesocycle	Preparatory Phase	High-Intensity Training Phase
Warm-up	General goals	Integrate autoregulation and ATOPE+ app use; Perform exercises with proper technique; Improve general fitness	Master autoregulation in high-intensity training; Maximize fitness state
	Components Aerobic	Relative intensity Zone 1–2[47,113]; Duration/volume 20–30 min continuous aerobic exercise	Relative intensity Zone 3–4[47,113]; Duration (min)/volume 10–20 min of low-volume, high-intensity interval training (SIT)
	Myofascial elasticity	Last 5° of participant's individual RoM; 2–3 exercises, 1–2 sets of 15 repetitions, 1 Hz	Last 5° of participant's individual RoM; 3–4 exercises, 2–3 sets of 15–20 repetitions, 1 Hz
Conditioning phase	Strength and power	Zone 1–2[114]; 8 exercise, 2–3 sets with a RIR > 6 repetitions[48]	Zone 3–4[114]; 8 exercises,1–4 sets with RIR < 6 repetitions[48]
Inter-Set Active Rest	Motor control upper quadrant	RPE < 3; 2 exercises of 60–90 s	RPE < 3; 2 exercises of 90–120 s
	Motor control lumbopelvic area	RPE < 3; 2 exercises of 60–90 s	RPE < 3; 2 exercises of 60–90 s
Recovery strategies	Myofascial release	—; 2 exercises of 2–3 min	—; 2 exercises of 3–5 min
	Myofascial stretching	To point of tightness; 4 exercises of 15–30 s	To point of tightness; 4 exercises of 30–50 s
	Breathing exercises	—; 8–10 min	—; 10–15 min

[a] ATOPE = Tailored Therapeutic Exercise and Recovery Strategies; RIR = repetitions in reserve; ROM = range of motion; RPE = rating of perceived exertion; SIT = sprint interval training.

117

physiotherapist expert in therapeutic exercise. Recovery strategies are followed at the end of each session (sessions last ≈1.5 h). Audiovisually-delivered dietary and tobacco avoidance recommendations are also provided. The program covers the recommended components for mitigating the side effects of treatment in patients with BC[35].

Following the principles of therapeutic exercise prescription[47], the program is tailored to each patient. It includes two training mesocycles: 1) a preparatory period of two weeks, three fixed sessions per week, of general training with linear prescription of moderate volume and low training load; and, 2) a high-intensity training period of 4-6 weeks, with 12-18 sessions, of non-linear prescription high-intensity training with daily load autoregulation[48] via the ATOPE+ app. Depending on the load assimilation (the patient's perceived recovery capacity, parasympathetic nervous system predominance, and other factors influencing recovery such as quality of sleep and psychological distress[49] collected in the app), ATOPE+ will generate a recommended daily workload for both aerobic and strength exercises. Low-volume high-intensity aerobic interval training (sprint interval training -SIT-), will be regulated via intensity and duration of the high-intensity intervals, and strength

exercises through intensity and volume (repetitions and sets). Aerobic exercise workload will be monitored through heart rate (HR) and a rating of perceived exertion (RPE) scale, and strength exercise through a modified repetitions in reserve (RIR) scale. The maximum interval between therapeutic exercise sessions is 3 days[50].

Sessions start with a warm-up followed by a conditioning period and finally a cooling-down period (Table 1). For the conditioning period, participants are allocated to appropriate training intensity zones[51]. Exercise sessions will require the availability of cross-trainer machines, isoinertial pulleys, kettlebells, dumbbells, jump boxes, fit balls, resistance bands, mats, and foam rolls.

STUDY DESIGN AND SETTING

The ATOPE trial (NCT03787966) will be conducted in two phases: a Feasibility Phase, followed by an Efficacy Phase. For the Feasibility Phase, 15 participants will follow the ATOPE-B program, and another 15 will follow the ATOPE-I program. This will help determine the feasibility of the main Efficacy Phase, and help consolidate the inclusion and exclusion criteria[52]. For the Efficacy Phase, a randomized, parallel-arm, superiority trial will be conducted with 29 participants per group, in which the effects of following ATOPE-B will be

compared to those of following ATOPE-I. Figure 2 provides an overview of the study.

All exercise sessions will be conducted at the CUIDATE unit (http://csaludable.ugr.es/pages/dossierultimo/%21), a cancer rehabilitation research unit of the Mixed University Sport and Health Institute (IMUDs), University of Granada.

Eligibility

The study will include women with newly diagnosed, histologically-confirmed, unresected stage I-IIIa BC. Besides, all must be: 1) >18 years old, 2) scheduled for surgery, chemotherapy and/or radiotherapy, 3) and be predisposed to developing cardiotoxicity, as described by
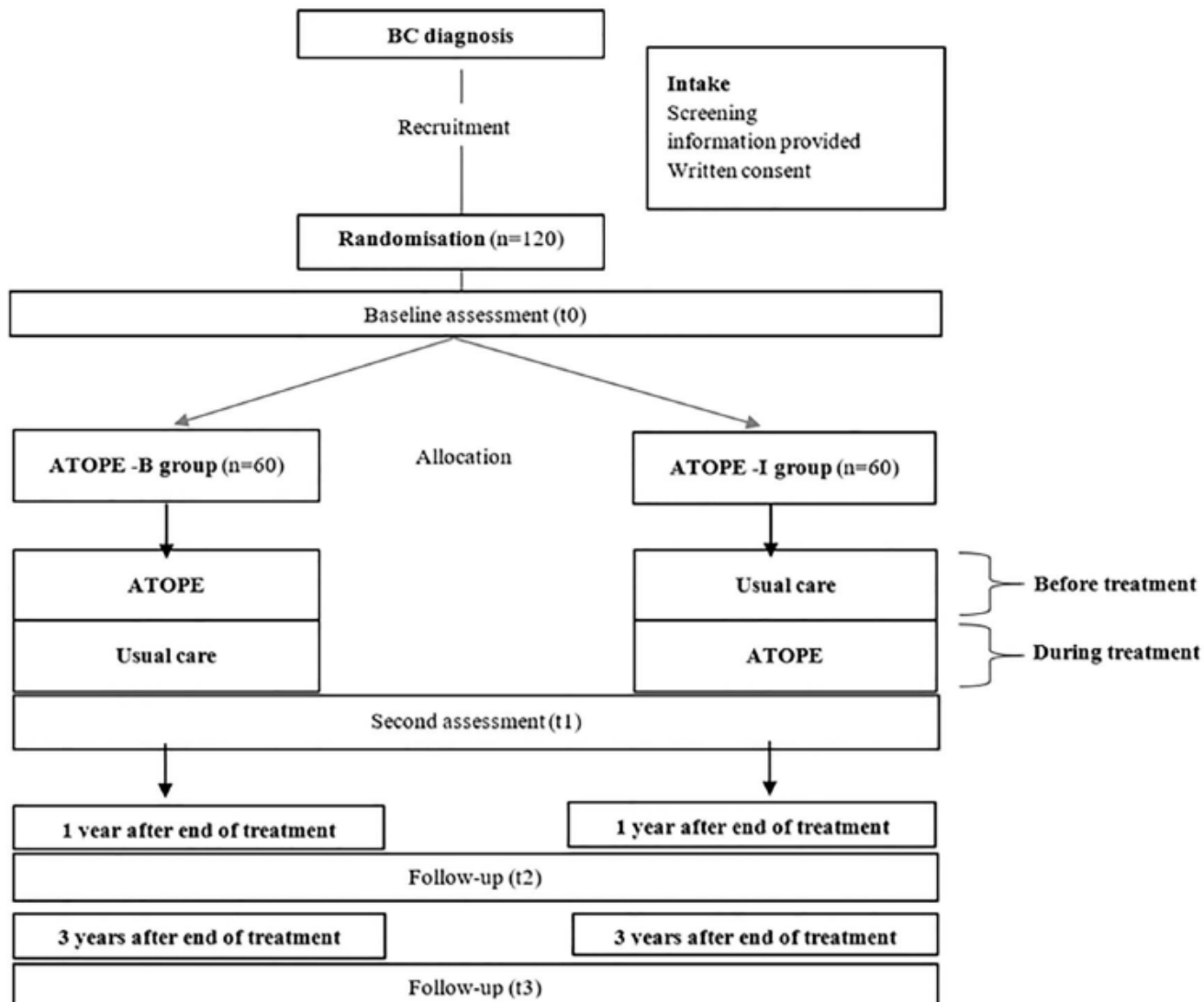
Figure 2. Overview of the study.

Table 2. Criteria Predisposing to Cardiotoxicity[15]

High-Dose Anthracycline[a]		
High-dose radiotherapy[b] where heart is in treatment field		
Lower-dose anthracycline[a]		Lower-dose radiotherapy[b] where heart is in treatment field
OR	AND	≥2 Cardiovascular disease risk factors[c] during or after completion of therapy
		Older age
Trastuzumab	Compromised cardiac function[d]	
Low-dose anthracycline[a] followed by trastuzumab		

[a]High-dose anthracycline (eg, doxorubicin $\geq$250 mg/m^2, epirubicin $\geq$600 mg/m^2); lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2). [b]High-dose radiotherapy ($\geq$30 Gy); lower-dose radiotherapy (<30 Gy). [c]Cardiovascular disease risk factors: smoking, diabetes mellitus, obesity, hypertension, dyslipidemia. [d]Compromised cardiac function (eg, borderline low [50%–55%] left ventricular ejection fraction, history of myocardial infarction, $\geq$ moderate valve disease at any time before or during treatment).

the American Society of Clinical Oncology Guidelines[15] (Table 2).

The exclusion criteria will be: 1) a previous history of malignancy, 2) having undergone previous treatment for cancer, 3) pregnancy, 4) having a psychiatric or cognitive disorder that prevents patients from following exercises correctly,

And/or acute or chronic condition that prevents exercise, and 5) any absolute contraindication for high-intensity exercise.

THE FEASIBILITY PHASE

Fifteen participants will be initially recruited to the Feasibility Phase[52] considering a minimum of 12 participants[53] and estimating a 25% of possible drop-outs[54].

Outcomes measures

Recruitment rate

This is the percentage of participants that meets the eligibility criteria out of the total number that provide consent and enrol after completing the baseline assessment. Fifteen participants will be initially recruited to the Feasibility Phase study. it will be considered feasible if at least 12 participants can be recruited to each arm in the Feasibility Phase[53].

Perceived health status change with the ATOPE program

This will be assessed using a Global Rating Changing scale with an intraclass correlation coefficient (ICC)=.90, minimal clinically important difference (MCID) of 2 points and a minimal detectable difference (MDD) of .45). This scale has been reported to have strong correlations with patient satisfaction measures (Spearman correlation coefficient .56-.77)[55] .

Adherence

Adherence is based on the proportion of participants that complete the intervention. Non-responders will be defined as change in endurance performance ≤0%. Both non-responders and reasons for missing sessions

120

will be recorded. The feasibility threshold for adherence in both arms will be 75%[56–58]. Participants will be encouraged through activity bracelets (Fitbit Inspire, Fitbit) to reach the minimum recommended levels of physical activity in a week (≥10 000 steps)[59].

Retention

This is the percentage of drop-outs and withdrawals over the ATOPE cycle. Reasons for withdrawals will be recorded. The feasibility threshold for retention in both arms will be 75%[54].

Safety and adverse effects

Participants will be interviewed periodically by a member of the research team to record the number of adverse effects. This will be done using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (v.5.0).

Barriers and facilitators

Possible barriers to, and facilitators of, the ATOPE exercises will be recorded[30] with a questionnaire with open-ended questions.

EFFICACY PHASE

Based on the results of a similar intervention study aim to detect a mean difference between ATOPE-B and ATOPE-I

of 5.06% of left ventricular ejection fraction (LVEF) (intervention group 64.88 ± 5.81 and control group 59.82±4.02)[60]. Assuming an α error of .05, a power of 90% and considering a large effect size of d=1 (based on the results of the reference study data) a minimum of 44 participants will be required for both arms (G*Power v. 3.1). Estimating a 30% of dropout-rate[54], in total, 58 patients will be recruited (29 in each group).

Recruitment

Oncologists, surgeons, and gynecologists will provide eligible patients from two hospitals: Breast Unit at the San Cecilio Hospital Health Campus, and the Virgen de las Nieves Hospital Radiotherapy and Oncology Service. Signed, informed consent will be required before undertaking any baseline assessment. All participants will undergo four assessment sessions (see below).

Randomization blinding and confidentiality

Participants will be randomly allocated to either the ATOPE-B or ATOPE-I arm (ratio 1:1) using block randomization (size of 4) with numbers generated by a computer running EPIDAT 4.2 software (Xunta de Galicia). The randomisation sequence will be prepared by a researcher with no clinical involvement in the study and will be the only one with access to it. Once patients are

evaluated, the assessors will notify the researcher who did the randomization and this one will tell the physiotherapist in charge of the program in which group that participant has been assigned.

All assessors and data analysers at all time points will be blind to the intervention group. Participants will be blind to the hypothesis of the study and will be encouraged to not reveal their group assignation to the assessor.

To maintain confidentiality, subject data will be identified by a coded ID number.

Outcome measures

Main outcome: Cardiotoxicity

This will be assessed via the LVEF using 2-D echocardiography[61] (employing a Samsung HM70A echograph and a Samsung Phased Array PE2-4 probe). The ICC=.92[62]. LVEF will be examined in the apical 4- and 2-chamber view using Simpson's biplane technique[63], with participants in the left lateral supine position[64]. The mean of two measurements will be used in analyses. The MDD is .09[65]. A reduction in absolute LVEF of ≥5% from baseline (i.e., measured at the time of diagnosis[66] will be deemed a sign of subclinical cardiotoxicity[67]; a reduction to <50% of the baseline value, or a 10% reduction from baseline, will be deemed to indicate cardiotoxicity[66,68]. A

122

cardiologist will be responsible for the correct execution of the test. The primary endpoint will be the comparison between the baseline and the 1-year follow up assessment.

Cardiovascular events that reflect toxicity

These will include periods of chest pain[69], breathlessness[70], arterial and pulmonary hypertension, supraventricular and ventricular arrhythmias, systolic and diastolic cardiac dysfunction[19].

Cardiac autonomic nervous system function

Time-domain (standard deviation of all NN intervals -SDNN-; the square root of the mean of the sum of the squares of differences between adjacent NN intervals -RMSSD-; number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording divided by the total number of NN intervals -pNN50-) and frequency-domain (power in the very low, low and high frequency range -VLF, LF, HF respectively-, the ratio LF/HF and Total Power) measures of the HRV[43] will be assessed by electrocardiogram (ECG), the gold standard for HRV measurements[71]. Measurements will be taken using a Norav DL800 Holter ECG monitor. HRV will be measured in the morning, after the bladder is emptied, with participants in a lying position[72]; measurements will be taken over 10 min, but only data for the last 5 min

interval will be used in analyses. Measurements of 5 min has been regarded reliable (ICC=.91)[73]. The MDD is 6.92 for RMSSD, 13.89 for LF, 13.86 for HF, 342.30 for Total Power[74]. The smallest worthwhile change (SWC) for resting vagal-related HRV indices are changes of ~+3%[75].

Patient-reported outcomes

Quality of life

This will be assessed using two questionnaires: 1) the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) v.3.0, commonly used to measure quality of life (QoL) in patients with cancer (test/retest reliability.82-.91)[76], and; 2) the European Organization for Research and Treatment of Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23), with Cronbach's α between .46 and .94[77].

Cancer treatment sessions

The following information will be collected: number of sessions received out of the total planned, delay of sessions, early session termination, treatment interruption (missing ≥3 consecutive sessions), time to treatment failure/discontinuation[78–80] (days from start to end of anticancer treatment if it was terminated for toxicity, tumor progression, other adverse effects

and/or any other reason), adverse effects, hospitalizations, and return to work[50] (recorded via the ATOPE+ app).

ATOPE sessions

All therapeutic exercise sessions modifications (≥1 session that requires a dose modification during the program, and number of sessions modified in total) and adverse effects (frequency of serious and non-serious events occurring during the program)[50] will be recorded via the ATOPE+ app.

Overall survival

The number of deaths per year and the number of participants alive at five years will be recorded.

Comorbidities

These will be recorded using the Charlson Comorbidity Index (Spanish version). The index predicts mortality via 17 comorbidities (with two subcategories), each with a weighted score of 1 to 6. A final score of 0 points = 12% mortality per year, 1-2 points = 26%, 3-4 points = 52%, and ≥5 points = 85%. The score will be corrected for age, adding 1 point for each decade following 50 years. The ICC is .91[81].

Physical outcomes

Cardiorespiratory fitness

VO2peak will be assessed via a cardiopulmonary exercise test with a Medisoft, 870 A treadmill and Jaeger MasterScreen® CPX gas analyser. The University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI) protocol[82] will be followed. Peak oxygen consumption will be calculated as the highest VO2 value in L/min during the test. The equation [(L/min × 1000)/ body weight (kg)] will be used to convert the value to mL·kg-1·min-1. The treadmill protocol and equation used is a valid method for determining VO2peak with a strong positive correlation with the American College of Sports Medicine's (ACSM) prediction equations (r=.9; P<.001)[82]. Cut-off points will be set at low (<13 ml·kg−1·min−1), moderate (13.9–16.9 ml·kg−1·min−1) and high (≥17 ml·kg−1·min−1)[83]. The MCID is a 6% of Vo2peak[84]. A specialist in sports medicine will be responsible for the correct execution of the test.

Strength

Handgrip strength will be assessed using a Takei TKK 5101 Grip-D digital dynamometer and leg, shoulder and abdominal strength using an isokinetic test with a Humac NORM isokinetic dynamometer. The handgrip strength test will be performed following a published protocol[85]. The test is reliable, has been validated for other populations[86], and has been previously used in patients with BC [87]. Shoulder strength will be measured via the maximal voluntary isometric contraction of the internal rotators in a position of 43º of internal rotation from the reference of a neutral shoulder flexion and rotation and a 90º elbow flexion for 6 s[88] (ICC .72-.94) [89]. Lower limb strength will be measured in the dominant leg, with 4 repetitions at 60º/s, 8 repetitions at 180º/s, and 15 repetitions at 300º/s. A warm-up will be performed, and a rest of 2 min allowed between sets[90–92] (ICC.74-.89)[89]. Abdominal strength will be measured via the isometric contraction of the trunk at 25º (three contractions of 5 s with 1 min rest between them) (ICC .87-.95[93]).

Flexibility

This will be assessed via the Chair sit-and-reach test. Two trials will be performed with each leg, the best value from each recorded, and the average for both legs included in the analysis. This test has an ICC of .96[94].

Anthropometric and body composition outcomes

Waist and hip circumferences

These will be measured using an inelastic tape. Waist circumference will be measured in the space between the last rib and the superior edge of the iliac crest; participants will be asked to breath normally and the

measurement taken at the end of the breath. Hip circumference will be measured at the greater trochanter level. The ICCs are .89 and .81 respectively[95].

Body composition

Fat mass, lean body mass, abdominal adipose tissue and body mass index (BMI; kg/m2) will be estimated using an InBody 720 impedanciometer[96]. This device provides reliable results[96].

Muscle quantity

Muscle thickness will be measured as a proxy of quantity of muscle; this will be determined using a Samsung HM70A echograph equipped with a Samsung LA3-16AD linear probe (6 MHz) following a protocol[97]. Ultrasound is a reliable and valid tool for muscle size assessment in older adults[98]. Sarcopenia will be deemed present when there is poor muscle function (<18 kg in handgrip test) and low muscle mass (<5.67 kg/m2)[99]. Cachexia will be defined as >5% weight loss over the past 6 months or a BMI of <20 kg/m2 with a weight loss of >2% in the last 6 months[100].

Biological and hormonal variables

Fasting blood samples will be collected at 8:00 a.m. by a trained nurse. Blood samples will be centrifuged at 2500 rpm for 15 min

(at 4ºC) and both the serum and erythrocyte fractions isolated and stored at -80ºC until use. Additionally, before centrifugation, an aliquot of 200 μL fresh blood will be separated for the estimation of the number of circulating immune cells. All selected measurements have high sensitivity and reproducibility in datasheets provided by manufacters.

Oxidative stress

Systemic oxidative damage to lipids, proteins and DNA will be assessed through the erythrocyte content of thiobarbituric acid reactive substances (TBARS), carbonyls and 8-hydroxy-2' -deoxyguanosine (8-OHdG) respectively. Additionally, total antioxidant capacity will be also estimated in the erythrocyte fraction; analyses will be performed using commercially available ELISA kits (Enzo Life Sciences, Inc., Farmingdale, NY, USA; Cell Biolabs, San Diego, CA, USA).

Inmune status

The percentage of CD 8 and 4 and regulatory T lymphocytes, and natural killer cells, will be measured in fresh blood via flow cytometry. This will be performed by a trained operator from the ibs.GRANADA technical platform, using commercially available kits (BD, Heidelberg, Germany).

Systemic inflammation

C-reactive protein (CRP), insulin-like growth factor 1 (IGF-1), interleukin (IL) 6 and 10, tumour necrosis factor alpha (TNF-α) will be analysed by commercially available kits (BD Biolegend, Heidelberg, Germany) using a FACSAria II 2L flow cytometer (BD, Heidelberg, Germany).

Other physiological variables

Blood glucose, lipids (cholesterol total, high-density lipoproteins and triglycerides), lactic acid and insulin levels will be assessed using standard techniques at hospital laboratories. Data regarding immunohistochemistry (IHC)-assessed expression of vascular endothelial growth factor (VEGF), p53 (tumour suppressor) gene mutations, the Ki-67proliferation index, E-cadherin production, oestrogen and progesterone receptors (ER and PR respectively), and of epidermal growth factor receptor 2 (HER-2) receptors, will be retrieved from clinical records (which contain the results of routine analyses of tumour biopsies).

Data collection and security

Participants will be assessed at four time periods (Fig. 1): at baseline (right after diagnosis) (t0), 3 days before the third chemotherapy session (t1)[101], one year (t2)[102], and three years (t3) after treatment ends. Assessments will be conducted over two days (≈90 min each day), with: 1) cardiac function and cardiopulmonary exercise tests on one day under the supervision of an expert cardiologist; 2) all other tests on the following day, under the supervision of a trained assessor from the research group.

To promote participant retention and thus maximise the data harvest, participants will be reminded of their assessment appointments via phone or e-mail as they prefer.

The mobile application will be installed manually in each participants' mobile phone and Patients' data will be gathered and stored meeting the European General Data Protection Regulation.

The server will be located within the facilities of the University of Granada (Granada, Spain) and its physical access will be limited to the researchers participating in the ATOPE project; besides, all the information stored will be pseudoanonymized and encrypted. This prevents unauthorized physical access to the data and the impossibility to read it without the necessary credentials for decryption.

All online communications of the ATOPE+ platform (ATOPE+ application and server) will be secured under HTTPS connections with SSL/TLS encryption.

126

Moreover, all the communications between the ATOPE+ app and the server will be tokenized under the OAuth 2.0 protocol to provide a secure delegated access for every patient enrolled in the trial. All communications with the database will be made locally through a secured (HTTPS) web application. A firewall will limit the number of available ports for connections, only enabling ports 22 (SSH) and 443 (HTTPS).

Data analysis in the two phases

Descriptive analysis will be used to summarize subject sociodemographic and clinical characteristics. Continuous variables will be expressed as mean ± standard deviation or mean (95% CI). Categorical variables will be expressed as numbers and percentages. The normal distribution of variables will be checked using the Kolmogorov-Smirnov test and visual inspection. For baseline comparisons, the Student t test will be used for continuous variables and the χ2 test for categorical variables; their non-parametric homologues, i.e., the Mann-Whitney U and Fisher's exact test, will be used as required. Significance will be set at p<.05. All calculations will be performed using the Statistical Program for the Social Sciences (IBM SPSS Statistic).

For the Feasibility Phase, proportions, percentages and paired-sample Student t test results will be reported.

For the Efficacy Phase, analysis of covariance (ANCOVA) will be used to assess the effects of the intervention on continuous variables; BMI, disease stage, type of medical treatment received, and physical activity performed outside the program will be considered as covariables. If an effect is detected, a post-hoc analysis with Bonferroni correction will be undertaken. All analyses will be 'intention-to-treat'. When data are missing, multiple imputation will be performed. Calculations of the intergroup effect sizes will be made to provide magnitude changes; the effect size will be estimated using Cohen's d (0–.19 negligible, .20–.49 small, .50–.79 moderate, ≥.8 large)[103].

DISCUSSION

The proposed trial should help clarify whether participating in a therapeutic exercise program before cancer treatment starts can mitigate cardiotoxicity better than the same kind of therapeutic exercise once treatment has already started. Therapeutic exercise training helps to prevent CVD in patients with BC during and after cancer treatment[30], but the effect of beginning such training before treatment starts remains unclear[104,105].

Comparison with prior work

Preclinical studies suggest cardiovascular training started before[31] and during[31,32] treatment for cancer to protect against cardiotoxicity. In rats, strength exercise may attenuate LV remodelling and cardiac dysfunction related to myocardial infarction[106]. Clinical studies in cancer populations are also beginning to suggest that pre-treatment therapeutic exercise may be cardioprotective[33,34,107]. Indeed, the evidence suggests that beginning a physical exercise program soon after diagnosis is associated with a reduction in cardiovascular events[108,109]. It is reported to have some positive effects on the cardiovascular system 24 h before chemotherapy[36], but no reduction in subclinical cardiotoxicity[37]. However, this may have to do with the dose of therapeutic exercise prescribed. The prescription of therapeutic exercise programs is still an area under development[30], but generic dosing does not seem optimal and can lead to overtraining[110]. Rather, it would appear that therapeutic exercise needs to be well structured and follow good prescription principles[47].

Recent research indicates that high doses of high intensity physical exercise may be beneficial[111], and it appears to be safe and feasible for patients with cancer[40].

The ATOPE program aims to personalise therapeutic exercise, and ensure optimal adherence through the use of new technologies[112] essential to the success of such a program[30].

Limitations

The trial suffers a number of limitations. Neither the participants nor the physiotherapist can be blind to the intervention, and differences in physical activity performed outside the program might be found between the treatment groups. However, data from the activity bracelets will be taken into account in analyses. To reduce adherence bias, a minimum 75% of attendance will be required for a subject's data to be included in analyses. Finally, to avoid HRV measurement bias, participants will attend an easy tutorial to ensure that they perform all measurements under optimal conditions.

Author Contributions

Concept/idea/research design: P. Postigo-Martin, R. Peñafiel-Burkhardt, T. Gallart-Aragón, F. Artacho-Cordón, N. Galiano-Castillo, L. Martín-Martín, S. Moreno-Gutiérrez, M. Arroyo-Morales, I. Cantarero Villanueva. Writing: P. Postigo-Martin, I. Cantarero Villanueva. Fund procurement: P. Postigo-Martin, M. Arroyo-Morales, I. Cantarero Villanueva. Providing

128

participants: M. Alcaide-Lucena, J. Ruiz-Vozmediano Providing facilities/equipment: M. Arroyo-Morales. Consultation (including review of manuscript before submitting): P. Postigo-Martin, R. Peñafiel-Burkhardt, T. Gallart-Aragón, F. Artacho-Cordón, N. Galiano-Castillo, C. Fernández-Lao, L. Martín-Martín, M. Lozano-Lozano, J. Ruiz-Vozmediano, R. Illescas-Montes, M. Arroyo-Morales, I. Cantarero Villanueva.

Ethics Approval

This study has the approval of the Biomedical Research Ethics Commit- tee (Granada, Spain) (0507-N-18, July 27, 2018). Prior to the start of the study, all participants will receive written and verbal information, and consent to be included will be obtained from all in concordance with the Declaration of Helsinki.

Clinical Trial Registration

ClinicalTrials.gov, NCT03787966 (December 21, 2019).

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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STUDY V

MHEALTH SYSTEM (ATOPE+) TO SUPPORT EXERCISE PRESCRIPTION IN BREAST CANCER SURVIVORS: A VALIDITY AND RELIABILITY, CROSS-SECTIONAL OBSERVATIONAL STUDY (ATOPE STUDY)

Not published (Submitted to Journal of Medical Systems)

STUDY V. MHEALTH SYSTEM (ATOPE+) TO SUPPORT EXERCISE PRESCRIPTION IN BREAST CANCER SURVIVORS: A VALIDITY AND RELIABILITY, CROSS-SECTIONAL OBSERVATIONAL STUDY (ATOPE STUDY)

ABSTRACT

Background: Physical exercise is already known to be beneficial for breast cancer survivors (BCS). However, avoiding overreaching is crucial in this population, as they are in a situation of physiological dysregulation. These alterations could lead BCS to decrease their exercise capacity or favour overreaching, which maintained over time, would increase their vulnerability to illness and death. The study aims to evaluate the validity and reliability of ATOPE+ mHealth system, to estimate autonomic balance and other wellness parameters that influence internal load, with the idea to facilitate nonlinear prescription, assessing readiness in BCS.

Methods: Twenty-two BCS were included in the validity and reliability analysis. The participants measured during four days morning autonomic balance, perception of recovery, sleep satisfaction, emotional distress and fatigue; with ATOPE+ mHealth system and with reliable comparison instruments.

Results: The validity results showed no significant differences, except for fatigue. The reliability results indicated an intraclass correlation coefficient (ICC) showed an excellent correlation for recovery (0.93; 95% CI 0.85-0.96) and distress (0.94, 95% CI 0.89-0.97) and good for LnRMSSD (0.87; 95% CI 0.74-0.94). Sleep satisfaction also showed excellent correlation with a Weighted kappa=0.83.

Conclusions: ATOPE+ is valid and reliable to remotely assess autonomic balance, perception of recovery, sleep satisfaction and emotional distress in BCS; however, it is not for fatigue. This highlights that ATOPE+ could be an easy and fast system used to assess readiness in BCS, and will help to improve their health, by supporting the prescription of optimal and safe physical exercise.

INTRODUCTION

Background

Physical exercise is already known to mitigate side effects of cancer and its treatment[1], reduce cancer recurrence[2,3], and mortality[2] in breast cancer survivors (BCS). In general, exercise should aim to achieve desired benefits, while balancing the risks of suboptimal loading, or overtraining. Avoiding overreaching or insufficient recovery would be important for BCS, as they are in a situation of physiological vulnerability due to cancer and its treatment. They have been through alterations such as increased oxidative stress[4], chronic inflammation[5], and reduced immune function[6]; that are similar to the alterations present in overtraining in athletes[7]. These alterations are related to side effects, but also may predispose these women to physiological dysregulation which maintained over time, would decrease their exercise assimilation capacity or even lead them to overreaching[8], and increasing their vulnerability to illness and death[9].

In oncology, the conventional prescription is linear, with a progressive and standard increase of intensity, frequency and duration parameters[10]. However, a nonlinear approach maximises the adaptation to exercise, which has been suggested to fit best to an optimal and safe dose-recovery period[10]. Ergo, could be safest to a heterogeneous population such as BCS. Also, it should be considered that in physical exercise programs the presence of no-responders[11], a wide range of adherence[12], and patients with comorbidities and higher toxicities[13], may challenge exercise prescription.

For this matter, nonlinear prescription is usually guided with methods such as the heart rate variability (HRV), which allows a better dose adjustment, and prevents overtraining[14]. Nevertheless, this has been commonly used in athletes, but its use is not as common in the clinical population (ClinicalTrials.gov Identifier: NCT03745742), and specifically the oncological, where the few experiences of prescribing are guided by symptoms[15]. Therefore, it is of great interest to develop an support tool like ATOPE+[16] to support a nonlinear prescription, monitor readiness, and control the loading-recovery cycle to allow safe and effective doses following physiological adaptations.

ATOPE+ mHealth system

When working with vulnerable population such as BCS, it is important to rely on validated tools. For instance, a previous example would be the BENECA app in BCS[17], which was successful in terms of

reliability[17] and efficacy[18]. BENECA records energy expenditure considering the exercise and food ingested, and recommends to increase or decrease physical activity in terms of energy balance. However, ATOPE+ is a step further in prescription, by saying whether they are physiologically ready and what dose is optimal for them. ATOPE+ is based on assessing autonomic balance with the HRV, as it reflects fatigue, stress and other factors which influence exercise assimilation[7]. However, as it has been stated that other internal load parameters are part of novel risks, or preclinical alterations preceding overtraining, such as poor sleep, worsened mood, stress, and increased fatigue[7]. These are especially important in patients with cancer and could mediate HRV themselves, so they are included as well in ATOPE+.

The gold standard for autonomic balance is the assessment of HRV with an electrocardiogram (ECG). However, for recovery and fatigue, there is a wide range of blood parameters such as blood lactate concentration[19] and creatine kinase (CK)[20]; for sleep analysis, the use of polysomnography; for stress, cortisol analysis[21], although they are not easily accessible, expensive, some are invasive, and time-consuming tests. For these reasons, we selected other instruments validated in previous studies as comparison

to validate ATOPE+. Therefore, ATOPE+ is HRV-guided but complemented with other internal load parameters, to remotely monitor the oncological population.

Aim

The aim of this study was to evaluate the validity and reliability of ATOPE+ to estimate autonomic balance and other wellness parameters that influence internal load, with the idea to facilitate nonlinear prescription, assessing readiness in BCS.

METHODS

A cross-sectional observational study was conducted to test the validity and reliability of ATOPE+ with 22 BCS.

Participants

Potential participants were identified from the referrals received from the Surgical Unit of the Hospital Universitario Clínico San Cecilio in Granada, Spain, in the period between February to August 2021. BCS were finally eligible if they had been diagnosed with breast cancer (Stages I-III); had basic abilities to use mobile apps; and had finished oncological treatment (hormonal treatment was not an exclusion criteria). In contrast, the potential participants were excluded if they had not finished chemotherapy or radiotherapy at the moment the study took place, had psychiatric or cognitive disorders, that

prevent from following the instructions of the protocol given, or did not have access to a smartphone.

Eligible women were asked to come to the CUIDATE group's facilities. A member of the research group explained the protocol of assessment and installed ATOPE+ in their phones. They were asked to use ATOPE+ in the presence of a researcher to ensure the correct assessment performance. They were also given the materials needed for remote assessment (ECG device, chest strap, questionnaires and assessments instructions).

Sample size

A sample size of 20 participants was estimated to be necessary to identify an intraclass correlation coefficient (ICC) of 0.8 between the LnRMSSD assessed with the Polar H10 chest band and the ECG (Gold Standard), 90% power, and an alpha error of 0.5[22]. Considering a potential 10% dropouts, 22 BCS were recruited for the study.

Description of ATOPE+ and data collection

To complete the study, patients had to take measurements with ATOPE+ and their comparison instruments, during four consecutive mornings, corresponding one of them to the weekend, in order to be as

precise to normal routine as possible. Patients were told to follow a normal sleep routine during the study. Once they have finished the app protocol, they continued filling the GS questionnaires given in paper format and sleep diaries. An overview of ATOPE+ mHealth system is shown in Figure 1.

ATOPE+ was developed by Biomedical (BIO-277) 'CUIDATE' research group and the Department of Computer Architecture and Technology, CITIC-UGR Research Centre, both from the University of Granada, Spain. The development of ATOPE+ is part of the ATOPE project, registration number NCT03787966 ClinicalTrials.gov, December 2019.

The ATOPE+ mHealth system is composed of a cross-platform app (Android/iOS) and a centralized secure server. The app provides patients with an interface to record their HRV, and to report their wellness through questionnaires. The centralized secure server enables data storage and processing, as well as the generation of tailored exercise prescription according to expert's rules. The architecture and usability of ATOPE+ have previously been described[16]. The registration code of the system is 1710092555522.

Once the research team has installed the app in the participant's phones and created their personal profiles, patients are ready to

start using the app. In the main view, patients can read a quick tutorial of how to perform the assessment or start it. The measurement starts once they push the button "Start", so they have to be prepared before pushing the button. The assessment of the HRV comes first. A notification with sound and vibration will alert that this first step is completed and can continue with the rest of the protocol.

Perceived recovery, sleep satisfaction and fatigue are assessed by horizontal continuous Likert scales from 0 to 10 with labels in the values at the extremes and a continuous slider are included in ATOPE+. For emotional distress, scale is positioned vertically. The final part of the assessment consists in performing 10 repetitions of the "Sit To Stand Test" (STS) and assessing the fatigue perceived after the effort with a rating of perceived exertion scale from 0 to 10. After that, the evaluation is completed. The answers are sent to the server and the participant receives an automatic personalized message about their readiness for either a high intensity session, a moderate one, or active recovery.

Comparison instruments

Autonomic balance

Autonomic balance was assessed with ATOPE+ with a Polar H10 chest strap (Polar H10, Polar Electro Oy, Kempele, Finland)

that connected through Bluetooth, and was compared with an ECG (Norav Holter DL800, Braemar Inc, Eagan, EEUU) monitor, considered the Gold Standard. From a 7-minute recording, the first and last minutes were cut off in order to achieve clear and precise interpretations of vagal tone with a 5-min signal, as recommended by the Task Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology[23]. The time domain parameter rMSSD (the square root of the mean squared differences) was analysed.

For ATOPE+, data was exported to a computer for its analysis. As recommended by the Taskforce, all artifacts (ectopic beats, arrhythmic events, and noise effects) in the RR time series were corrected or removed, to reduce the chances of substantial deformities that can occur in HRV analysis[24]. In the case of Holter data, software NH300 (Norav, version 2.70) was used to perform the spectral analysis by using Fast Fourier transform algorithms to remove noise from recordings. Sampling rate was of 128 samples/second. Frequency filter was set from 0.05 to 60 Hz. Due to low sampling rate, the software itself applied an interpolation algorithm in order to improve R peaks' detection[25].

After waking up and emptying their bladder, participants were instructed to moisten and

place the chest band and the ECG monitor. Then, lying on their beds facing the ceiling, data recording was performed under the same terms of duration for both devices.

Recovery

The Perception of Recovery Scale was used as comparison to assess the perception of recovery. It is a subjective self-administered Likert-type scale with punctuations from 1 to 10, and with a sensitivity and specificity of 0.82 and 0.81, respectively[26].

Sleep

As comparison, the subsection of quality of sleep from the consensus sleep diary, a reliable tool for prospectively measure quality of sleep[27] was used. It is a self-reported method that includes quantitative and qualitative aspects related to each night of rest. This method, compared to polysomnography, has a Kappa Coefficient of 0.87[28].

Emotional Distress

The Emotional Distress thermometer according to "The NCCN Clinical Practice Guidelines in Oncology", was used as comparison to measure emotional distress. This tool consists of a Likert-type scale with values from 0 to 10, where 0 is "no emotional distress" and 10 constitutes "extreme emotional distress". In the Spanish oncology population, this thermometer has a sensitivity of 0.9 and a specificity of 0.64[29].

Peripheral Fatigue

The Borg-CR 10 scale was used as comparison for the evaluation of the perceived level of fatigue after physical exertion. After performing 10 repetitions at a rhythm of 40 beats per minute (marked by a metronome included in ATOPE+) of the STS, a test frequently used as a protocol to induce fatigue in the lower extremities, participants completed this questionnaire, which consists of scores from 0 to 10 ("Not at all"- "Very, very hard", respectively). This scale has a reliability of 0.66 according to the Kappa coefficient in clinical population of women[30].

Statistical Analysis

The IBM SPSS version 24 was used for all analyses (IBM Statistical Program for Social Sciences SPSS Statistic, Corp., Armonk, New York). For Bland-Altman analyses, Excel worksheets (Microsoft Excel version 16.55, Microsoft, Washington, EEUU) was used. A 95% Confidence Interval (CI) was established; and significance was set at $p<0.05$. Imputation methods were used for missing data.

A descriptive analysis was performed to summarize sociodemographic and clinical characteristics of participants. Continuous variables were expressed as mean ±

144

standard deviation, and categorical variables as number and percentage. The normal distribution of the variables was checked by means of the Shapiro-Wilks test. Data that didn't follow a normal distribution were transformed in Ln(x) or Ln(x+1) to enable parametric analysis. All analyses were carried out by a blinded researcher.

Validity

To determine the validity of ATOPE+, paired samples t-test were conducted comparing ATOPE+ measurements versus reliable measurements. Continuous variables were analysed by Student's t-test in case of normal parametric variables, and nonparametric variables with Wilcoxon test. Considering that they only reflect proportional relationships and can cause erroneous interpretation of measurements, in order to establish the agreement between the comparison instruments and ATOPE+ methods, Bland-Altman analyses also were carried out, which allow us to see the difference between two clinical measurement devices, against each method's mean. To obtain further information, sleep satisfaction was treated as a continuous variable for this purpose. In order to establish inter-devices agreement, Cohen's d for effect size was used, being effect sizes categorised as: 0 to 0.19, trivial; 0.2 to 0.59, small; 0.6 to 1.19, moderate; 1.2 to 1.99, large; and >2.0, very large[31].

Wilcoxon rank test and effect size were calculated for ordinal variables.

Reliability

For each outcome measure, concordance between comparison instruments and those included in ATOPE+ was calculated. Bearing in mind that Pearson correlation coefficients, paired t test, and Bland-Altman plots are methods for analysing agreement but not ideal in terms of reliability[32], inter-device ICC were calculated to reflect relative reliability. If ICC scores were considerate as poor (<0.5), moderate (0.5-0.75), good (0.75-0.90) and excellent (>0.90)[33]. Weighted kappa was used for categorical variables. The suggested interpretation for agreement is as follows: ≤0 poor, .01–.20 slight, .21–.40 fair, .41–.60 moderate, .61–.80 substantial, and .81–1 almost perfect[34]. In order to express absolute reliability, the typical error of measurement (TEM) was calculated. These kinds of calculations identified with-in subject variation for each method, indicating the magnitude to which repeated measures changed for participants.

RESULTS

Sample description

A total of 22 BCS were recruited for the study. Finally, of the participants, 1 could not be included in the sample because was

not able to complete the four days of measurement for personal issues. The mean age of the participants was of 49.48

chemotherapy, radiotherapy all together as treatment (63.64%).

Table 1. Demographic characteristics (n=22)

Characteristic		Participants
Age (years), mean (SD)		49.48 (8.38)
Race, n (%)		
	Caucasic	20 (90.91)
	Other	1 (4.55)
	Missing	1 (4.55)
Social situation, n (%)		
	Married	14 (63.64)
	Single	4 (18.18)
	Divorced	2 (9.10)
	Widowed	1 (4.55)
	Missing	1 (4.55)
Occupation, n (%)		
	Currently working	5 (22.73)
	Her duties	3 (13.64)
	Current sick leave	4 (18.18)
	Unemployed	6 (27.27)
	Retired	1 (4.55)

Abbreviations: SD: standard deviation.

(SD 8.38) years. Tables 1 and 2 summarizes demographic and clinical characteristics of the participants. Of the participants, 6 (27.27%) were unemployed. Most participants had had stage II breast cancer (36.36%) and had undergone surgery,

Validity

Validity analysis outcomes are shown in Table 3. Paired sample T-test revealed significant differences for fatigue (p<.001). The strongest parameter agreement for ATOPE+ compared to comparison

146

Table 2. Clinical characteristics (n=22)

Characteristics		Participants
Menopause, n (%)		
	Premenopause	9 (40.91)
	Postmenopause	12 (54.55)
	Missing	1 (4.55)
Medical treatment, n (%)		
	Surgery and chemotherapy	2 (9.10)
	Surgery and radiotherapy	3 (13.64)
	Surgery, chemotherapy and radiotherapy	14 (63.64)
	Missing	1 (4.55)
Cancer stage, n (%)		
	I	5 (22.73)
	II	8 (36.36)
	III	4 (18.18)
	Missing	5 (22.73)

instruments was the mean Emotional Distress, with a Pearson correlation of 0.91. In contrast, the weakest parameter agreement with a Pearson correlation of 0.80 was found in LnRMSSD (Table 3).

Bland-Altman plots were also generated (Figure 2a-e), being a graphical representation to depict the difference and limits of agreement between ATOPE+ mean measurement methods and comparison instruments mean measurement methods. Bland Altman bias, with 95% limits of agreement (LOA), 95% CIs and effect sizes are shown in Table 3. Effect size was small for all variables except for fatigue which was large.

Reliability

Interclass Correlation

The ICC for each comparison instrument and ATOPE+ methods showed evidence of good reliability, being all values higher than 0.86 (Table 4). Sleep satisfaction showed a strong correlation (Weighted kappa=0.87).

Table 3: Indices of validity for ATOPE+ mHealth system in BCS (N=22)

	ATOPE+ (mean± SD)	Comparison instruments (mean ± SD)	p value	Bias (LOA)	Pearson/Spearman Correlation (r)	Effect size
LnRMSSD (ms)						
	3.79± 0.44	3.94±0.42	0.070	-0.12 (-0.60 to 0.26)	0.80	-0.379 (-0.818, 0.068)
Recovery Perception (points, Likert scale)						
	5.93±1.62	5.61±1.86	0.19	0.24 (-1.39 to 1.88)	0.88	0.283 (-0.157, 0.716)
Sleep satisfaction (%)						
Very bad	1 (4.55)	1 (4.55)	0.157	-	0.81	-0,308*
Bad	1 (4.55)	1 (4.55)				
Fair	12 (54.55)	14 (63.64)				
Good	6 (27.27)	3 (13.64)				
Excellent	1 (4.55)	2 (9.091)				
Missing	1 (4.55)	1 (4.55)				
Emotional distress (points, Likert scale)						
	2.75±2.4	2.55±2.39	0.22	0.20 (-1.22 to 1.62)	0.91	0.244 (-0.193, 0.676)
Fatigue (points, Likert scale)						
	3.67±2.22	2.41±2.19	<.001	1.25 (-0.80 to 3.31)	0.88	1.323 (0.724, 1.905)

LnRMSSD, mean square root differences of the standard deviation

Table 4: Indices of reliability of ATOPE+ mHealth system for mean HRV parameter, recovery, sleep, emotional distress and fatigue of breast cancer survivors (n=22)

	Mean TEM (95% CI)	Mean ICC (p), (95% CI)
Mean LnRMSSD		
	0.069 (-0.26 to -0.02)	0.87 (0.74 to 0.94)
Mean recovery		
	0.19 (-0.65 to 0.14)	0.93 (0.85 to 0.96)
Mean sleep		
	-	0.83[a]
Mean emotional distress		
	0.059 (-0.02 to 0.22)	0.94 (0.89 to 0.97)
Mean fatigue		
	0.06 (0.22 to 0.48)	0.86 (0.29 to 0.95)

TEM, typical error of measurement (95% confidence interval); ICC, intraclass correlation coefficient (95% confidence interval); LnRMSSD, natural logarithm of the mean square root differences of the standard deviation. [a]Weighted kappa

148

DISCUSSION

Our findings showed that ATOPE+ is valid and reliable to assess autonomic balance, perception of recovery, sleep satisfaction and emotional distress in BCS. However, it was not for detecting fatigue. These results highlight that ATOPE+ could be an easy and fast system to measure tailored readiness in BCS, and a tool to improve health by helping professionals to prescribe optimal and safe exercise doses. Moreover, ATOPE+ may provide reliable data-driven analysis with machine learning algorithms, as originally described in its architecture[16].

Comparison with prior work

The majority of previous work is not oriented to the clinical population, but to athletes[35] to avoid overtraining[14] and increase performance[36]. In the clinical population, to our knowledge a similar tool has not been developed, although there is an ongoing one on post myocardial infarction (ClinicalTrials.gov Identifier: NCT03745742), with less demanding purpose but more oriented to improve functional capacities and reducing fatigue. To our knowledge, there is not an application that has been yet specialized in the readiness in the oncological population, in particular, in women with BCS, that has HRV as the principal assessment but complemented with other internal load parameters.

Regarding the validity observed in HRV parameters, the results from ATOPE+ were similar to those in the literature[35,37]. On the one hand, these positive results in ATOPE+ regarding HRV, were expected as the Polar H10 chest band, which has already had excellent results in the literature[38]. In the study by Gilgen-Ammann et al.[38] they found that it has excellent validity compared to an ECG monitor, and recommended it as gold standard, especially during exercise, as it surpassed the ECG in terms of inducing less recording noise. Besides good results in our study could have been due to the patients being instructed that it was of great importance to empty their bladder, to remain still during the measurement, to breathe normally, and to have a comfortable environment without distractions. Nevertheless, correlation was expected to be higher. These results could be obtained because the software that automatically analyses ECG data, could not be using the same interpolation methods, or selection of outliers or ectopic beats. On the other hand, for the Bland-Altman analysis, previous studies[35,37] obtained a higher percentage of values of HRV outside the limits of agreement. ATOPE+ reduced percentage of values outside the levels of agreement for HRV could have been the result of the application having a timer that told participants where to stop both devices at the same time, as longer samples had been identified to modify HRV indexes[23].

Considering the rest of the parameters, we could find significant differences between the fatigue measured with ATOPE+ and the Borg scale, but not for the rest of the internal load parameters. Therefore, it may not be useful for detecting fatigue. Patients were instructed to immediately fill the questionnaires in paper, however, the time in between could explain the differences, because as time passes, the perceived fatigue decreases[39]. Also, another possible hypothesis is that maybe ATOPE+ fatigue scale should be complete with more verbal anchors, facilitating patients' answer, or it could be due to differences in the formats used. Therefore, we still wanted to address that even if criteria validity was not met, analysis was performed until the end and found excellent correlation results. In the future, we could add more anchor words, or turn the scale horizontal to try to investigate this difference. However, as recovery could be seen as inversely proportional to fatigue, it could be still recognised that having the recovery data may be sufficient from a clinical point of view.

Limitations and strengths

The system is aimed at BCS and not patients with other types of cancer. Patients had to have basic mobile phone capabilities. Besides, ATOPE+ may be restricted to the available technology, even if not particularly expensive, could not be accessible for everyone (Polar H10 chest band). The system is only supported in smartphones but not in tablets or computers, and some sight problems in elderly patients could demand family support. Besides, Spanish is the only available language of the system. Also, a limitation is that we did not include biomarkers that could support the results, as we wanted a fully non-invasive assessment. In the future, we could establish new tools for different cancer types, have English as an available language, include photoplethysmography for greater accessibility to the population, and include invasive biomarkers as an optional complement to ATOPE+.

ATOPE+ also presents some strengths. The system could be a very powerful tool for professionals as it may guarantee safe exercise doses. Also, it saves time as readiness or recovery could be assessed remotely. Besides, it is a step towards health monitoring and involves patients to be part of it, and may help them learn to regulate recovery. Also, it is a friendly, easy to install and use app, compatible with both Android and IOS systems, so it can reach a population with less mobile phone capabilities.

Clinical implications

ATOPE+ can be an excellent support tool to exercise programs in BCS, optimising

physical exercise, improving adherence and safety. Also, it offers professionals a single, easy, remote and validated tool that assesses several parameters related to different systems, and could identify risk profiles and target interventions to a particular problem. Lastly, it can be used together with other complementary tools, as it is not time consuming and does not require patients to wear any device.

Conclusion

ATOPE+ is a valid and reliable tool to monitor readiness in BCS which could help rehabilitation professionals to prescribe safer and optimal doses of exercise. It ensures that BCS have an adequate recovery period to induce compensations ensuring meeting the principles of training. As a new technology, it offers a more easy, fast and inexpensive way of doing so. ATOPE+ is a valid and reliable tool to assess autonomic balance, sleep satisfaction, emotional distress in BCS. Therefore, it could be an excellent tool to support physical exercise programs in this population by assessing readiness.

DECLARATIONS

Ethics approval and consent to participate

This study has the approval of the Biomedical Research Ethics Committee

(Granada, Spain) (0507-N-18, July 27, 2018). All participants received written and verbal information, and consent to be included was obtained from all in concordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

PPM, ICV, MAM, and SMG conceptualized the study and wrote the manuscript. AGS, MLG, and RGG performed statistical analyses and wrote the manuscript. PPM, MLG, and AGS recruited and measured patients with cancer and healthy matched controls. PPM and SMG created the database. All the authors analysed and interpreted the data and revised and edited the manuscript for submission.

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LIMITACIONES GLOBALES

GLOBAL LIMITATIONS

LIMITACIONES GLOBALES

Esta tesis se ha desarrollado en un contexto determinado en el que se presentaban una serie de limitaciones que, si bien se han ido mencionando previamente, es necesario resumirlas en este apartado.

Primeramente, nos encontramos con que los resultados del test de evaluación de la capacidad funcional, para monitorizar el posible deterioro de las pacientes, se realizaron en una población muy concreta: mujeres con cáncer de mama activas, que se encontraban o recibiendo el tratamiento oncológico o en el periodo de supervivencia, por lo que habría que comprobar la generalización de los resultados a grupos con otras características, y por tanto, hay una limitación en cuanto a la validez externa.

Seguidamente, analizar grupos de pacientes que estaban en diferentes momentos de su fase de tratamiento, limita el análisis de cambios longitudinales. Aunque tal y como se muestra, los grupos no mostraban diferencias en variables caracterizadoras. Por ello, sería interesante llevar a cabo diseños longitudinales, pero también explorar más tipos de cáncer y las secuelas y situación de salud de estos pacientes al diagnóstico. Por otro lado, aunque la valoración del estado de salud es bastante amplia, no se han introducido variables que

podrían influir en los resultados, como la fatiga y la depresión, o las alteraciones del sueño, alteraciones previas, otras comorbilidades u otros factores biopsicosociales. Sin embargo, este estudio surgió para dar respuesta a planteamientos previos y destaca la importancia de mejorar la evidencia manifestada por investigaciones de ciencia básica y explorar posibles alteraciones clínicas presentes en el momento del diagnóstico; y por tanto poder orientar las intervenciones desde ese momento antes de que el tratamiento médico agrave el estado de estos pacientes.

La revisión sobre el efecto del ejercicio terapéutico en la cardiotoxicidad tiene como principal limitación que hay escasos estudios que han sido publicados en la literatura al respecto, por lo que las conclusiones extraídas han de ser tomadas con cautela, e impide una selección única para una dosis óptima de ejercicio. Además, sería preciso añadir que, desde su realización, ha habido un aumento del número de publicaciones sobre el tema, por lo que sería necesaria una actualización de esta información.

Respecto al planteamiento del protocolo para determinar una intervención para determinar una intervención adecuada en estos pacientes, la limitación más importante puede ser que las personas con menos manejo de tecnología pudieran

tener problemas a la hora de usar la aplicación; sin embargo, ésta es muy intuitiva e integra instrucciones para asegurar la correcta medición diaria. Además la aplicación cuenta con un protocolo auxiliar, que además de ser explicado al paciente y familiares, va integrado dentro de la aplicación y puede ser consultado previa medición. Durante la validación de la aplicación, además nos hemos encontrado con algunas limitaciones como el que sólo se encuentre en castellano, que esté dirigida a pacientes con cáncer de mama exclusivamente, que no incluya fotopletismografía o el espacio para introducir biomarcadores complementarios, por lo que se podría abordar en futuras versiones de esta.

FUTURAS LÍNEAS

DE INVESTIGACIÓN

FUTURE

DIRECTIONS

FUTURAS LÍNEAS DE INVESTIGACIÓN

Partiendo de lo abordado en esta Tesis Doctoral, se proponen diferentes líneas de investigación que irían dirigidas a aumentar el conocimiento de la prevención de secuelas en pacientes oncológicos y dar respuesta a algunas necesidades aún presentes.

- Analizar el estado de salud de forma lo más detallada posible de pacientes con cáncer recién diagnosticados, para poder establecer intervenciones de forma temprana y un correcto seguimiento durante las intervenciones, para poder prevenir o mitigar de forma óptima las toxicidades de los tratamientos del cáncer o futuros tratamientos y alteraciones que produzcan derivadas de ellas.

- Por otro lado, se ha planteado la introducción de otros grupos de pacientes con mayor fragilidad, que podrían tener mayores complicaciones en el ciclo dosis-recuperación, como mujeres con cáncer de mama en estadios avanzados, cáncer de pulmón y población infantil.

- Por otro lado, se pretende seguir colaborando con especialistas en cardiología, para identificar biomarcadores que permitan detectar toxicidad de forma más inmediata, en un momento subclínico.

- Finalmente, aunque la aplicación ATOPE+ cumple con los objetivos marcados, sería interesante poder perfeccionarla y mejorarla, además de hacer de ATOPE+ una herramienta más completa en la que se puedan incluir recomendaciones escritas y audiovisuales, con demostraciones en vídeo.

CONCLUSIONES

CONCLUSIONS

CONCLUSIONES

Conclusiones Generales

Los resultados de esta Tesis Doctoral refuerzan el conocimiento sobre la presencia de secuelas en pacientes con cáncer, antes, durante y después de los tratamientos. En el momento del diagnóstico, los pacientes con cáncer colorrectal pueden mostrar signos que reflejan un estado de hiperalgesia primaria o sensibilización central, junto con un deterioro del estado físico y composición corporal; bien por el propio cáncer, otras comorbilidades y algunos estilos de vida inadecuados.

Por otro lado, con respecto a la cardiotoxicidad, una de las secuelas más importantes en esta población, se ha mostrado en estudios preclínicos que la prevención es factible a través del ejercicio físico. Sin embargo, no hay suficiente evidencia a nivel clínico, y se requiere determinar las dosis óptimas para pacientes con diferentes características. El protocolo ATOPE se desarrolla para intentar mostrar la eficacia de un programa de ejercicio individualizado y adaptado a la dosis-recuperación, y ATOPE+ es una herramienta que es válida y fiable que se ha desarrollado con el propósito de asistir en el programa. Este programa puede ser un abordaje importante para una dosificación óptima y

segura de ejercicio terapéutico, para prevenir la toxicidad antes o durante el tratamiento, antes de que las secuelas se instauren.

Conclusiones Específicas

Las principales conclusiones específicas que se derivan de esta Tesis Doctoral son las siguientes:

Sección 1: Herramientas para el seguimiento del estado de salud física en supervivientes y evaluación del estado de salud de los pacientes con cáncer recién diagnosticados.

1. La valoración de la capacidad funcional al a través del test de los 6 minutos en cinta permite detectar pacientes con deterioro cuando presentan una diferencia mínima clínicamente significativa de aproximadamente 54 metros en pacientes durante el tratamiento, y de 40,95 metros después del tratamiento.

2. Antes del comienzo del tratamiento, los pacientes recién diagnosticados de cáncer presentan alteraciones que pueden agravarse con los tratamientos. En concreto, hemos encontrado que los

pacientes recién diagnosticados presentan signos de hiperalgesia primaria y de sensibilización central, además de alteraciones en el estado físico y composición corporal en el momento del diagnóstico. Por tanto, evaluar el estado de salud al diagnóstico es crucial

segura, es válida y fiable para evaluar el balance del autónomo, la percepción de recuperación, la satisfacción con el sueño y el distrés emocional; sin embargo, no la fatiga.

Sección 2: Ejercicio terapéutico como herramienta para la prevención de toxicidad.

3. El ejercicio terapéutico muestra efectos positivos para la prevención o mitigación de alteraciones cardiovasculares del tratamiento médico en mujeres con cáncer de mama. Aunque el ejercicio físico se ha mostrado factible y seguro, no se ha podido esclarecer una dosis clara dirigida a la cardioprotección en esta población.

4. Un programa de ejercicio terapéutico antes o durante el tratamiento médico (ATOPE) podría mitigar los efectos cardiotóxicos de estos en mujeres con cáncer de mama.

5. La herramienta ATOPE+ para el soporte de una dosis de ejercicio terapéutico óptima y

CONCLUSIONS

General conclusions

The results of this Doctoral Thesis reinforce that alterations are present in cancer patients, before, during and after treatments. At diagnosis, patients with colorectal cancer may show signs of primary hyperalgesia or central sensitization, together with a deterioration of physical condition and body composition; either due to the cancer itself, other comorbidities and an unhealthy lifestyle.

Moreover, regarding cardiotoxicity, one of the most important side effects in this population, it has been shown in preclinical studies that prevention is feasible through physical exercise. However, there is insufficient evidence at a clinical level, and optimal doses need to be determined for patients with different characteristics. The ATOPE protocol is developed to try to show the efficacy of a therapeutic exercise program that follows a dose-recovery tailored prescription; and ATOPE+, which is a valid and reliable tool that has been developed for the purpose of assisting in the program. This program may be an important approach for optimal and safe dosing of therapeutic exercise, to prevent toxicity before or during treatment, before the onset of side effects.

Specific Conclusions

The main specific conclusions derived from this Doctoral Thesis are the following:

Section 1: Tools for monitoring physical health status in survivors and assessing the health status of newly diagnosed cancer patients.

1. The assessment of functional capacity with the 6-minute walking test on treadmill, allows detecting a decline when they present a minimum clinically significant difference of approximately 54 meters in patients during treatment, and of 40.95 meters after treatment.

2. Prior to the start of treatment, newly diagnosed cancer patients present alterations that may be aggravated by the treatments. Specifically, we have found that newly diagnosed patients present signs of primary hyperalgesia and central sensitization, in addition to alterations in physical status and body composition at diagnosis. Therefore, assessing health status at diagnosis is crucial.

Section 2: Therapeutic exercise as a tool for the prevention of toxicity.

3. Therapeutic exercise shows positive effects for the prevention or mitigation of cardiovascular alterations of medical treatment in women with breast cancer. Although physical exercise has been shown to be feasible and safe, a specific dose aimed at cardioprotection in this population has not been yet clarified.

4. A therapeutic exercise program before or during medical treatment (ATOPE) could mitigate the cardiotoxic effects of medical treatment in women with breast cancer.

5. The ATOPE+ mobile health system for optimal and safe therapeutic exercise dose support, is valid and reliable tool for assessing autonomic balance, perception of recovery, sleep satisfaction, and emotional distress; but not fatigue.

ANEXOS

ANEXES

Artículos derivados de la Tesis Doctoral Internacional

En este apartado se presentan los trabajos derivados de la presente tesis doctoral, ya previamente incluidos en el apartado de material y métodos, resultados y discusión. Se incluyen tres trabajos que han sido publicados (portada y última página), y dos que se encuentran en fase de revisión y no están aceptados aún a fecha de elaboración de tesis.

1. Cantarero-Villanueva I, Postigo-Martín P*, Granger CL, Waterland J, Galiano-Castillo N, Denehy L. The minimal clinically important difference in the treadmill six-minute walk test in active women with breast cancer during and after oncological treatments. Disability and Rehabilitation. 2022 (accepted, in press).

2. Lopez-Garzon M, Postigo-Martin P*, González-Santos Á, Arroyo-Morales M, Achalandabaso-Ochoa A, Férnández-Pérez AM, Cantarero-Villanueva I. Colorectal cancer pain upon diagnosis and after treatment: a cross-sectional comparison with healthy matched controls. Support Care Cancer. 2022 Apr;30(4):3573-3584. doi: 10.1007/s00520-022-06803-2.

3. Postigo-Martin P, Galiano-Castillo N, Lozano-Lozano M, González-Santos A, Lopez-Garzon M, Peñafiel-Burkhardt R, Cantarero-Villanueva I. Cardiotoxicity and therapeutic exercise in breast cancer: effects and dose. Systematic review and meta-analysis (under review in Scientific Reports).

4. Postigo-Martin P, Peñafiel-Burkhardt R, Gallart-Aragón T, Alcaide-Lucena M, Artacho-Cordón F, Galiano-Castillo N, Fernández-Lao C, Martín-Martín L, Lozano-Lozano M, Ruíz-Vozmediano J, Moreno-Gutiérrez S, Illescas-Montes R, Arroyo-Morales M, Cantarero-Villanueva I. Attenuating Treatment-Related Cardiotoxicity in Women Recently Diagnosed With Breast Cancer via a Tailored Therapeutic Exercise Program: Protocol of the ATOPE Trial. Phys Ther. 2021 Mar 3;101(3):pzab014. doi: 10.1093/ptj/pzab014.

5. Postigo-Martin P, Gil-Gutiérrez R, Moreno-Gutiérrez S, López-Garzón M, González-Santos A, Arroyo-Morales M, Cantarero-Villanueva I. (Enviado a Journal of Medical Systems)

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ORIGINAL ARTICLE

The minimal clinically important difference in the treadmill six-minute walk test in women with breast cancer during and after oncological treatments

Q2 Irene Cantarero-Villanueva[a,b,c] , Paula Postigo-Martin[d,b,c] , Catherine L. Granger[e,f] , Jamie Waterland[g], Noelia Galiano Castillo[a,h] and Linda Denehy[i,j,k]

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ABSTRACT

Purpose: To examine the minimal clinically important difference (MCID) in the treadmill 6-minute walk test (6MWT) in women with breast cancer.

Materials and methods: A secondary analysis of cross-sectional data from 112 women who were undergoing chemotherapy or had undergone anticancer treatment was conducted. Participants completed the 6MWT on a treadmill and the European Organization for Research and Treatment of Cancer Questionnaire (EORTC-QLQ-C30) twice, eight weeks apart. Change in the physical function domain of the EORTC-QLQ-C30 was used to classify the "positive change" subgroup ($\geq$5 points difference) and the "unchanged" subgroup ($<$5 points difference). This was combined with the distance difference from the 6MWTs, determining the MCID as the cut-off from the area under the receiver operating characteristic (AUROC) curve (anchor-based determination). The MCID was also determined from (1) the effect size and (2) the difference in standard error (SEM) of the results of the first and second 6MWT (distribution-based determination).

Results: The MCIDs in the during-chemotherapy group was (effect size-based and SEM-based) 66.5 and 41.5 m respectively and those in the after-treatment group to be 41.4 and 40.5 m

Conclusions: The MCID in the treadmill 6MWT distance could be used to interpret changes in the physical health status of women with breast cancer.

> ➤ **IMPLICATIONS FOR REHABILITATION**
> - The MCID for the 6MWT on treadmill in active women with breast cancer is of approximately 54 m during chemotherapy, and 41.5 m after treatment.
> - The MCID on treadmill 6MWT distance could be used to interpret a decline in the physical health status of women with breast cancer.
> - The 6MWT on treadmill could be an easy, feasible, performed under controlled conditions, alternative to the 6MWT to obtain valuable information in this population.

Introduction

Breast cancer and its treatment have important impacts on women's health, including physical and psychological alterations [1] and even loss of functional capacity [2]. Functional capacity is the ability to perform activities of daily living. Particularly important among them is the ability to walk since it facilitates self-sufficiency and provides information about the state of the cardiopulmonary [3] and musculoskeletal systems [4]. The 6-min walk test (6MWT) – a submaximal walking test – is commonly used to determine functional exercise capacity in patients with different ailments, including cancer [5]. Indeed, it is often used in rehabilitation in oncology patients since it is easily performed [5] and

provides prognostic and survival information [6], and key information is provided by the minimal clinically important difference (MCID) in the walked distance.

The MCID is the smallest change required to affect patient-perceived outcomes and, hence, reflects whether the change is relevant [7]. The MCID is valuable to patients with cancer, clinicians and researchers, and allows interpretation of any change in performance of the 6MWT. Identification of reference values that highlight changes in patients' health with cancer is essential to analyse trends in recovery and to provide adequate interventions. This will help to offer a continuum cancer care to prevent physical deterioration [8]. Anchor- and distribution-based methods are the

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ORIGINAL ARTICLE

Colorectal cancer pain upon diagnosis and after treatment: a cross-sectional comparison with healthy matched controls

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Abstract

Background The current study sought to explore whether cancer pain (CP) already exists in patients at colorectal cancer (CRC) diagnosis before treatment compared with patients with colorectal cancer (CRC) after treatment and a healthy matched control group. The study also sought to examine whether factors related to physical health status could enhance pain processes.

Methods An observational cross-sectional study was conducted following the STROBE checklist. Twenty-nine newly diagnosed and forty post-treatment patients with CRC and 40 healthy age/sex-matched controls were included for comparison. Pain, local muscle function, and body composition outcomes were assessed by a physiotherapist with > 3 years of experience. ANCOVA and Kruskal–Wallis tests were performed, with Bonferroni and Dunn-Bonferroni post hoc analyses and Cohen's d and Hedge's effect size, as appropriate.

Results The analysis detected lower values of pressure pain threshold (PPT) points, the PPT index, and abdominal strength and higher values of self-reported abdominal pain in newly diagnosed patients, with even more marked results observed in the post-treatment patients, where lower lean mass and skeletal muscle index values were also found than those in the healthy matched controls ($p < 0.05$). In the post-treatment and healthy matched control groups, positive associations were observed between the PPT lumbar dominant side points and abdominal isometric strength and lean mass, and negative associations were observed between the lumbar dominant side points and body fat ($p < 0.05$).

Conclusion Upon diagnosis, patients with CRC already show signs of hyperalgesia and central sensitization and deteriorated physical conditions and body composition, and this state could be aggravated by subsequent treatments.

Keywords Body composition · Cancer pain · Colorectal cancer · Muscle strength · Pain measurement

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Introduction

Cancer pain (CP) is one of the most prevalent and concerning aspects of the disease that patients with cancer must face, and it occurs in more than 60% of patients across all cancer stages [1], even from diagnosis [2]. This pain is very difficult to manage because it is a poorly understood and undertreated syndrome [3] that involves crucial health expenditures [4].

A systematic classification of chronic pain was developed by the International Association for the Study of Pain (IASP) that distinguishes chronic primary and chronic secondary pain syndromes. When pain persists or recurs for more than 3 months, it is considered chronic pain. In some conditions where pain may be considered a disease, the term chronic primary pain is used. However, in other cases, pain is secondary to an underlying disease, such

177

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Attenuating Treatment-Related Cardiotoxicity in Women Recently Diagnosed With Breast Cancer via a Tailored Therapeutic Exercise Program: Protocol of the ATOPE Trial

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Abstract

Objective. Therapeutic exercise is already used to ameliorate some of the side effects of cancer treatment. Recent studies examined its preventive potential regarding treatment-related toxicity, which can increase the risk of functional decline and lead to disease recurrence and death. This trial will examine whether the Tailored Therapeutic Exercise and Recovery Strategies (ATOPE) program, performed before treatment, can mitigate the onset and extent of cardiotoxicity beyond that achieved when the program is followed during treatment in recently diagnosed breast cancer patients.

Methods. The intervention has a preparatory phase plus 12 to 18 sessions of tailored, high-intensity exercise, and post-exercise recovery strategies. A total of 120 women recently diagnosed with breast cancer, at risk of cardiotoxicity due to anticancer treatment awaiting surgery followed by chemotherapy and/or radiotherapy, will be randomized to either group. In a feasibility study, measurements related to recruitment rate, satisfaction with the program, adherence to them, the retention of participants, safety, and adverse effects will be explored. In the main trial, the efficacy of these interventions will be examined. The major outcome will be cardiotoxicity, assessed echocardiographically via the left ventricular ejection fraction. Other clinical, physical, and anthropometric outcomes and biological and hormonal variables will also be assessed after diagnosis, after treatment, 1 year after treatment ends, and 3 years after treatment ends.

Conclusion. Given its potential effect on patient survival, the mitigation of cardiotoxicity is a priority, and physical therapists have an important role in this mitigation. If the ATOPE intervention performed before treatment returns better cardioprotection results, it may be recommendable that patients recently diagnosed follow this program.

Impact. The ATOPE program will highlight the need for a physical therapist intervention from the moment of diagnosis, in the prevention or mitigation of cardiotoxicity, in women with breast cancer. It could help physical therapists to establish an adequate therapeutic exercise dose adapted to breast cancer patients and to propose correct therapeutic exercise prescription according to the assimilation of the sessions.

Keywords: Breast Neoplasms, Cardiotoxicity, Mobile Application, Physical Therapy, Prehabilitation, Therapeutic Exercise, Recovery Strategies

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SHORT CURRICULUM VITAE

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Education

2018-2022	PhD Student in Clinical Medicine and Public Health, University of Granada, Spain
2017	Master degree in Basic and Applied Neuroscience and Pain, Universidad de Granada
2016	Master degree in Advanced Manual Therapy, University of Jaen
2015	Degree in Physiotherapy, University of Jaen

Professional positions

2021-2022	Predoctoral Researcher – FPU research fellowship. Department of Physiotherapy. University of Granada, Spain.
2021	Temporary teacher. Department of Physical Therapy. University of Granada, Spain.
2018-2021	Predoctoral Researcher – FPU research fellowship. Department of Physiotherapy. University of Granada, Spain.

Grants

2018-2022	Research Fellowship: Formación de Profesorado Universitario (FPU). Spanish Ministry of Education, Culture and Sports, Spanish Government, Spain.
2021	International Research Internship Fellowship: Movilidad de Formación de Profesorado Universitario (FPU Movilidad). Spanish Ministry of Education, Culture and Sports, Spanish Government, Spain.

Supervision

2021	Supervisor for six graduate Thesis (Graduate Degree in Physiotherapy, University of Granada, Spain.
2018-2021	Supervisor of six master Thesis (Master degree in Manual and Invasive Physiotherapy, University of Granada, Spain).

International internships

2021-2022   Faculty of Medicine, Department of Physical Therapy, University of British Columbia, Vancouver, Canada. Professor Kristin Campbell.

Research projects

2021-curr.   Efectividad de un Sistema e-HEALTH Integrado en un Programa de Recuperación Física para el Tratamiento del Dolor en la Población Oncológico. PaiNEd Study. **82.906€**. Consejería de Salud y Familias – Junta de Andalucía.

2019-curr.   Efectos sobre la Aparición de la Toxicidad producida por el tratamiento Oncológico mediante un Programa de Ejercicio terapéutico adaptado (ATOPE): ensayo clínico controlado, aleatorizado en mujeres con cáncer de mama. **99.220€**. Instituto de Salud Carlos III.

2020-curr.   Ajustando la dosis de ejercicio terapéutico para prevenir la neurotoxicidad causada por el tratamiento para el cáncer. **19.980€** Asociación Española Contra el Cáncer.

2021   Equilibrio Redox en pacientes de cáncer de mama y la contribución del estado físico y psicosocial. Comparación con mujeres sanas pareadas por edad. **2.800€**. Ilustre Colegio Profesional de Fisioterapeutas de Andalucía. **IP: Paula Postigo Martín**.

2021   Contribución del estado físico y psicológico en el equilibrio REDOX en mujeres con cáncer de mama. Comparación con mujeres sanas pareadas por edad. **1.700€.** Plan Propio de la universidad de Granada. **IP: Paula Postigo Martín.**

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1. Ortiz-Comino L, Galiano-Castillo N, **Postigo-Martin P**, González-Santos A, Lopez-Garzon M, Martín-Martín L, Fernández-Lao C. Factors influencing quality of life in survivors of head and neck cancer: a preliminary study. Semin Oncol. 2022. In press.

2. Salinas-Asensio MDM, Ocón-Hernández O, Mundo-López A, Fernández-Lao C, Peinado FM, Padilla-Vinuesa C, Álvarez-Salvago F, **Postigo-Martín P**, Lozano-Lozano M, Lara-Ramos A, Arroyo-Morales M, Cantarero-Villanueva I, Artacho-Cordón F. 'Physio-EndEA' Study: A

Randomized, Parallel-Group Controlled Trial to Evaluate the Effect of a Supervised and Adapted Therapeutic Exercise Program to Improve Quality of Life in Symptomatic Women Diagnosed with Endometriosis. Int J Environ Res Public Health. 2022;19(3):1738. doi: 10.3390/ijerph19031738.

3. Lopez-Garzon M, Cantarero-Villanueva I, González-Santos A, **Postigo-Martin P**, Lozano-Lozano M, Galiano-Castillo N. Can physical exercise prevent chemotherapy-induced peripheral neuropathy in patients with cancer? A systematic review and meta-analysis. Arch Phys Med Rehabil. In press.

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7. Castro-Martín E, Galiano-Castillo N, Fernández-Lao C, Ortiz-Comino L, **Postigo-Martin P**, Arroyo-Morales M. Myofascial Induction Therapy Improves the Sequelae of Medical Treatment in Head and Neck Cancer Survivors: A Single-Blind, Placebo-Controlled, Randomized Cross-Over Study. J Clin Med. 2021 Oct 27;10(21):5003. doi: 10.3390/jcm10215003.

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Randomized Controlled Trial. J Med Internet Res. 2020 Mar 10;22(3):e16258. doi: 10.2196/16258.

16. Rico-Villademoros F, **Postigo-Martin P**, Garcia-Leiva JM, Ordoñez-Carrasco JL, Calandre EP. Patterns of pharmacologic and non-pharmacologic treatment, treatment satisfaction and perceived tolerability in patients with fibromyalgia: a patients' survey. Clin Exp Rheumatol. 2020 Jan-Feb;38 Suppl 123(1):72-78.

17. Ariza-Garcia A, Lozano-Lozano M, Galiano-Castillo N, **Postigo-Martin P**, Arroyo-Morales M, Cantarero-Villanueva I. A Web-Based Exercise System (e-CuidateChemo) to Counter the Side Effects of Chemotherapy in Patients With Breast Cancer: Randomized Controlled Trial. J Med Internet Res. 2019 Jul 24;21(7):e14418. doi: 10.2196/14418.

18. Lozano-Lozano M, Cantarero-Villanueva I, Martin-Martin L, Galiano-Castillo N, Sanchez MJ, Fernández-Lao C, **Postigo-Martin P**, Arroyo-Morales M. A Mobile System to Improve Quality of Life Via Energy Balance in Breast Cancer Survivors (BENECA mHealth): Prospective Test-Retest Quasiexperimental Feasibility Study. JMIR Mhealth Uhealth. 2019 Jun 25;7(6):e14136. doi: 10.2196/14136.

Congress communications

The PhD candidate will highlight the communications with relation with the doctoral thesis:

ATOPE: Non-linear multimodal program and mobile application to mitigate cardiotoxicity. Feasibility and preliminary effects. 2020 American College of Sports Medicine Annual Meeting, World Congress on Exercise is Medicine, and World Congress on the Basic Science of Exercise and Vascular Health. San Diego Convention Center in San Diego, CA (Accepted, yet to be held May 31 to June 4, 2022)

Comparación del estado físico en mujeres con cáncer de mama a lo largo de las diferentes etapas del tratamiento. (Proyecto ATOPE). III Congreso Internacional del Colegio Oficial de Fisioterapeutas de Canarias, Ejercicio Terapéutico = Salud, celebrado los días 20-22 de septiembre de 2019 en Santa Cruz de Tenerife.

Ajustando la dosis de ejercicio terapéutico para prevenir la toxicidad en el sistema nervioso causada por el tratamiento médico para el cáncer en mujeres con cáncer de mama. Protocolo de un ensayo clínico controlado aleatorizado. 4º Congreso Español de la mama, celebrado los días 17-19 de octubre de 2019 en Madrid.

Other research merits

Reviewer for 2 JCR journals.

2020-curr.   Member of the research group PAIDI BIO-277, in the line of Physical Exercise and Cancer research, University of Granada, Spain.

2018-curr.   Member of the "Sport and Health University Research Institute (iMUDS)", University of Granada, Spain.

2018-curr.   Member of the Instituto de Investigación Biosanitaria ibs.Granada, Granada, Spain.

Teaching experience

Degree of Physiotherapy, University of Granada, Spain.

2021-2022   Fundamentals of Physiotherapy (5.6 ECTS Credits).

Physiotherapy Methods in Vascular and Urogynecologic Pathology. (3.5 ECTS Credits).

2020-2021   Fundamentals of Physiotherapy (5 ECTS Credits).

Assessment in Physiotherapy (1 ECTS Credits).

Electrotherapy and Thermotherapy (1,5 ECTS Credits).

Physiotherapy in Neurologic Pathology (2 ECTS Credits).

2019-2020   Fundamentals of Physiotherapy (4 ECTS Credits).

Physiotherapy in Sports (2 ECTS Credits).

2018-2019   Movement therapy (4 ECTS Credits).

Assessment in Physiotherapy (2 ECTS Credits).

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