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PROGRAMA OFICIAL DE DOCTORADO EN MEDICINA CLÍNICA Y SALUD PÚBLICA
UNIVERSIDAD DE GRANADA

DESCRIPCIÓN DEL DOLOR Y EL TONO VAGAL EN MUJERES SUPERVIVIENTES DE CÁNCER DE MAMA Y EFECTOS FÍSICOS DE UN PROGRAMA DE FISIOTERAPIA ACUÁTICA

PAIN DESCRIPTION AND VAGAL NERVE ACTIVITY IN BREAST CANCER SURVIVORS AND PHYSICAL EFFECTS OF AN AQUATIC PHYSIOTHERAPY PROGRAM

Facultad de Ciencias de la Salud
Departamento de Fisioterapia

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CERTIFICA:

Que la Tesis Doctoral titulada "*Descripción del dolor y el tono vagal en mujeres supervivientes de cáncer de mama y efectos físicos de un programa de fisioterapia acuática*" que presenta Dª . **ELENA CARO MORÁN** al superior juicio del Tribunal que designe la Universidad de Granada, ha sido realizada bajo mi dirección durante los años 2013-2015, siendo expresión de la capacidad técnica e interpretativa de su autora en condiciones tan aventajadas que le hacen merecedora del Título de Doctora con mención Internacional, siempre y cuando así lo considere el citado Tribunal.

Fdo. Dra. Dª. Lourdes Díaz Rodríguez

En Granada, a 11 de mayo de 2015

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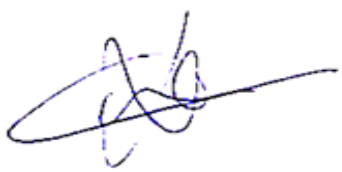
Fdo. Dra. Dª. Carolina Fernández Lao



En Granada, a 11 de mayo de 2015

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RESUMEN

El diagnóstico precoz, los avances en los tratamientos y la prevención de la recurrencia son factores responsables del aumento de la supervivencia en las pacientes de cáncer de mama. Estas pacientes sufren numerosas secuelas o trastornos crónicos relacionados con la propia enfermedad o derivadas de los tratamientos recibidos que repercuten sobre su calidad de vida. Las mujeres supervivientes de cáncer de mama (SCM), objeto de nuestro estudio, presentan disfunciones cardíacas, dolor y falta de movilidad en las extremidades superiores y cuello, obesidad y fatiga.

Los objetivos principales de esta tesis han sido, analizar la variabilidad de la frecuencia cardíaca (VFC) a partir de un electrocardiograma calculando el tiempo entre los intervalos RR de dos latidos consecutivos, describir el dolor musculoesquelético y neuropático mediante el estudio de los umbrales del dolor a la presión y tests de neurodinamia, y por último, evaluar la efectividad de un programa de fisioterapia acuática sobre el dolor articular asociado a la hormonoterapia en mujeres supervivientes de cáncer de mama.

Un total de 106 pacientes de cáncer de mama y 66 mujeres sanas que cumplieron con los criterios de inclusión, formaron parte de los diferentes estudios que componen esta Tesis Doctoral.

Los principales resultados y conclusiones de esta tesis son: 1) las SCM presentan un aumento de la frecuencia cardíaca en reposo y niveles más bajos de la VFC; 2) hipersensibilidad neural bilateral y generalizada, además de una reducción del rango de movilidad articular del lado afecto de las pacientes; 3) procesos de sensibilización central determinados por una hiperalgesia bilateral generalizada en el cuello y en la región frontal y dorsal del hombro; 4) reducción de los umbrales del dolor a la presión y de la circunferencia de la cintura tras un programa de ejercicio acuático en SCM con artralgia asociada a la terapia hormonal.

Esta memoria de Tesis Doctoral ayuda a comprender la importancia de analizar los posibles desequilibrios cardiovasculares provocados porel cáncer y sus tratamientos mediante la VFC y a esclarecer los mecanismos de producción del dolor musculoesquelético y neural relacionados con el cáncer de mama. Además, trata de demostrar que un programa de fisioterapia acuática puede ser eficaz para reducir los umbrales del dolor a la presión en mujeres SCM con artralgia asociada a la terapia hormonal.

ABSTRACT

Early diagnosis, advances in treatments and prevention of recurrence are responsible factors of the increase of survival in patients with breast cancer. These patients suffer numerous side effects or chronic conditions related to the disease itself or derived from the treatments received and impacting their quality of life. Breast cancer survivors (BCS), object of our study, present heart disorders, pain and reduced mobility in the upper limbs and neck, obesity and fatigue.

The principal aims of this thesis were to analyze the heart rate variability (HRV) calculated from electrocardiogram records as the time interval between consecutive heartbeats (RR intervals), describe the musculoskeletal and neuropathic pain by studying pressure pain thresholds and neurodinamic tests, and finally evaluate the effectiveness of aquatic physical therapy on joint pain associated to hormone therapy program in BCS.

A total of 106 breast cancer patients and 66 healthy women who met inclusion criteria were involved in different studies that make up this Doctoral Thesis.

The main results and conclusions of this thesis are: 1) BCS present an increase in resting heart rate and lower levels of HRV; 2) bilateral and generalized neural hypersensitivity, along with a reduction in joint range of motion of the affected side in patients; 3) central sensitization processes determined by a generalized bilateral hyperalgesia in the neck and the front and back shoulder region; 4) reduced pressure pain thresholds and waist circumference after aquatic exercise program in BCS with hormone therapy-associated arthralgia.

This Doctoral Thesis helps to understand the importance of analyzing the potential cardiovascular imbalances caused by cancer and its treatments through HRV and clarify the mechanisms of production of the musculoskeletal and neural pain related to breast cancer. Also, it tries to show that an aquatic physiotherapy program can be effective in reducing pressure pain thresholds in BCS with hormone therapy-associated arthralgia.

A

ABREVIATURAS
ABBREVIATIONS

ABREVIATURAS/ ABBREVIATIONS

AI	Aromatase Inhibitors
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BCS	Breast Cancer Survivors
BMI	Body Mass Index
CI	Confidence Interval
CIF	Cancer-Induced Fatigue
ECG	Electrocardiogram
FIC	Fatiga Inducida por el Cáncer
HF	High Frequency
HRV	Heart Rate Variability
IA	Inhibidores de Aromatasa
LF	Low Frequency
MET	Metabolic Equivalent of Task
NN	Normal to Normal
NPRS	Numeric Pain Rating Scale
PPT	Pressure Pain Threshold
RHR	Resting Heart Rate
RMSSD	Root Mean Square of Successive Differences
ROM	Range of Motion
RR	R wave to R wave
SCM	Supervivientes de Cáncer de Mama
SD	Standard Deviation
SDNN	Standard Deviaton of NN intervals
UDP	Umbrales del Dolor a la Presión
ULNT	Upper Limb Neurodynamic Test
VFC	Variabilidad de la Frecuencia Cardíaca

I

INTRODUCCIÓN
INTRODUCTION

INTRODUCCIÓN

El cáncer es la principal causa de muerte en los países económicamente desarrollados, la segunda causa de muerte en los países en desarrollo[1], y a escala mundial, el cáncer causa más muertes que todas las enfermedades coronarias o todos los accidentes cerebrovasculares[2]. El cáncer es una enfermedad cuya incidencia está aumentando; según la Organización Mundial de la Salud se prevé que la incidencia de las enfermedades oncológicas en la población mundial aumente un 75% con 22 millones de nuevos casos estimados para el año 2030[3]. Esta incidencia es también cada vez mayor en los países en vías de desarrollo económico como resultado del envejecimiento de la población y el crecimiento, así como la adopción de hábitos de vida asociados con el cáncer, como son el tabaco, la inactividad física y las dietas occidentalizadas[4].

En España, en el año 2012 la incidencia del cáncer fue de 215.534 casos, y el número de muertes fue de 102.762 casos, con un 10,2% de riesgo de fallecer antes de los 75 años. La predicción para este año 2015, según la Sociedad Española de Oncología Médica, es de 227.076 nuevos casos de cáncer y 108.390 muertes a causa de esta enfermedad[5].

El cáncer de mama es el segundo cáncer más frecuente a nivel mundial (1,7 millones de casos, 11,9%) después del cáncer de piel, y el quinto como causa de muerte (522.000, 6,4%) debido al pronóstico relativamente favorable[2]. El cáncer de mama es el más frecuente entre las mujeres occidentales[6]. En España se diagnostican alrededor de unos 22.000 nuevos casos de cáncer de mama al año[7,8], en concreto, la mayor incidencia, mortalidad y prevalencia a 5 años es para este tipo de cáncer (29%, 15,5% y 40,8%, respectivamente)[5]. En España, la tasa de incidencia del cáncer de mama desde 1980, ha aumentado en un 2,9% anual[9]. Y a pesar de que esta incidencia aumenta lentamente[10,11], la tasa de mortalidad disminuye de forma considerable[12]. En nuestro país el índice de supervivencia está en el 85% a los cinco años de la intervención[13], algo más alto que en el resto de Europa. El aumento de la supervivencia es atribuible a las mejoras en los tratamientos[14,15], la prevención de la recurrencia[16] y el diagnóstico precoz[13,17], transformando a estas pacientes oncológicas en pacientes con secuelas o trastornos crónicos[18].

Las mujeres supervivientes de cáncer de mama (SCM), objeto de nuestro estudio, experimentan uno o más síntomas relacionados con el cáncer, y padecen secuelas físicas y

psicológicas relacionadas algunas con el tratamiento que reciben, y otras, como consecuencia de la falta de movilidad y dolor que aparece después de la cirugía del cáncer[19], e inevitablemente esta situación repercute de forma negativa sobre la calidad de vida de las mismas[20].

Variabilidad de la Frecuencia Cardíaca en Mujeres Supervivientes de Cáncer de Mama

Las mismas terapias agresivas y prolongadas[15] que han reducido la tasa de mortalidad por cáncer de mama, también se asocian con efectos adversos, como el deterioro de la función cardiopulmonar[21]. Las antraciclinas, fármacos quimioterapéuticos ampliamente prescritos en el tratamiento del cáncer de mama, tienen efectos cardiotóxicos permanentes; las terapias con anti-HER2 son responsables de la disfunción cardíaca transitoria reversible, y los fármacos utilizados en el tratamiento hormonal alteran el metabolismo lipídico, aumentando la cardiotoxicidad de éstos cuando se combinan diferentes tratamientos[22]. Por otra parte, la radioterapia también puede aumentar el riesgo de padecer enfermedades cardíacas[23]. Los efectos cardiotóxicos de los tratamientos oncológicos pueden afectar a la actividad vagal y por lo tanto, influyen en el balance autonómico cardíaco[22,23].

El desequilibrio vegetativo a largo plazo está asociado con un mayor riesgo de enfermedad cardiovascular y a una mayor mortalidad[24]. Parece haber una relación bidireccional entre desequilibrio autonómico y cáncer. Scott et al[21] documentaron recientemente que las señales de las células tumorales se transmiten a través de vías humorales y nerviosas al cerebro, lo que le confiere a éste, la capacidad de modular el sistema psiconeuroendocrino inmunológico para regular el crecimiento tumoral en los tejidos periféricos. Por el contrario, la disfunción autonómica cardiovascular es común en diferentes tipos de cáncer y conlleva un aumento del tono simpático y una disminución del tono vagal[25]. La actividad nerviosa vagal involucrada en la función del nodo sinusal modula los mecanismos claves para el desarrollo y la progresión del cáncer (estrés oxidativo, daño celular del ADN, reacción inflamatoria, y la respuesta excesiva del sistema nervioso simpático). De Couck, Mravec y Gidron[26] encontraron que una actividad vagal adecuada favorece un mejor pronóstico en las pacientes de cáncer de mama.

La variabilidad de la frecuencia cardiaca (VFC) es un importante indicador no invasivo de la respuesta nerviosa vagal y un potencial marcador de estrés[27], siendo además una prueba útil

para evaluar estados de desequilibrio vegetativo[28]. El índice de VFC se define como la variación de la frecuencia del latido cardiaco durante un intervalo de tiempo definido con anterioridad (nunca superior a 24 horas) en un análisis de períodos circadianos consecutivos. Mediante un electrocardiograma se detectan las ondas R y se calcula el tiempo entre las diferentes ondas R consecutivas o intervalos RR. La VFC es el resultado de la interacción entre el Sistema nervioso autónomo y el sistema cardiovascular[29,30]. El sistema nervioso simpático y parasimpático, principales responsables de los cambios en el intervalo entre latidos, modifican la frecuencia cardiaca y pueden cuantificarse mediante el dominio de tiempo de la VFC y el dominio de frecuencia[31].

Según el Colegio Americano de Cardiología y la Asociación Americana del Corazón, los pacientes oncológicos que han recibido quimioterapia, especialmente con antraciclinas, altas dosis de ciclofosfamidas o trastuzumab, representan un grupo de alto riesgo (Etapa A) para la insuficiencia cardíaca[32]. Las investigaciones han demostrado que los tratamientos coadyuvantes para el cáncer reducen los valores de VFC después de la cirugía[33], la radioterapia[34], y la quimioterapia[35].

Un pronóstico correcto es crucial en el tratamiento del cáncer, y la rutina de los tests de VFC pueden ser útiles para la toma de decisiones clínicas y gestión de la enfermedad[36,37]. Una baja actividad del tono vagal en los pacientes oncológicos puede actuar como factor de riesgo, mientras que una alta actividad jugaría como papel protector[26]. De hecho, algunos investigadores han observado niveles más bajos de VFC en los estadios más avanzados en diferentes tipos de cáncer[38,28,39,40].

Existe poca información sobre el equilibrio del sistema nervioso vegetativo durante la fase inicial de supervivencia en pacientes con cáncer de mama. Actualmente desconocemos que haya estudios controlados que comparen los valores de VFC entre SCM en el primer año de post-tratamiento y mujeres sanas.

Estudio de los mecanismos del dolor en el Cáncer de Mama

Un gran número de SCM presentan comorbilidades en las extremidades superiores como pueden ser dolor postquirúrgico, enfermedad del manguito rotador, epicondilitis lateral, capsulitis adhesiva, artralgias, radiculopatía cervical, plexopatía braquial, neuropatía, síndrome de dolor postmastectomía, linfedema, síndrome del hueco axilar, trombosis venosa profunda[41] y movilidad

reducida[42]. Este problema puede aparecer inmediatamente después de la cirugía de cáncer de mama o pocos años después[43,44]. Este trastorno doloroso reduce el funcionamiento físico y tiene como resultado efectos psicosociales adversos con consecuencias significativas de carácter negativo en la calidad de vida[45,46]. La incidencia del dolor varía desde el 25 hasta el 60% en las SCM[47,48] y el 12-29% de las pacientes informan dolor atribuido al cáncer después de un periodo superior a 6 años[49].

El tratamiento estándar de cirugía de mama, radioterapia y quimioterapia neurotóxica tienen una relación complicada con los trastornos neuromusculares, musculoesqueléticos y linfovasculares. Las etiologías específicas de dolor inducido por el tratamiento del cáncer de mama son complejas. La disección axilar puede causar disfunción del nervio periférico y la formación de tejido cicatricial[50]. La radioterapia puede causar plexopatía braquial[51,52], y esta plexopatía braquial inducida por la radiación puede ser debida al daño del nervio o a la compresión de las fibras nerviosas a través de la fibrosis del tejido conectivo axilar y supraclavicular[51]; este daño neural se ha asociado con déficits sensoriomotores y funcionales[53]. Además, la exposición a la quimioterapia neurotóxica puede inducir neuropatía periférica[54,55], aumentando el riesgo del daño del plexo braquial. Diferentes factores tales como la interrupción del transporte axoplasmático, o la degeneración axonal o daños a las células nerviosas sensoriales están relacionados con la fisiopatología de este fenómeno[56], que puede hacer los nervios más susceptibles a la compresión crónica[57]. Por otro lado, estudios anteriores han descrito hipersensibilidad del dolor a la presión, es decir, el aumento de la sensibilidad al dolor en el miembro superior como signo de un mecanismo de sensibilización central en las mujeres después del tratamiento estándar del cáncer de mama, concretamente, la combinación de la disección axilar, la radioterapia y la quimioterapia[18].

Si bien es cierto que el mecanismo que implica la función del daño a los nervios en el proceso de sensibilización central en SCM aún no está claro, se han desarrollado diferentes estudios con pruebas basadas en la estimulación mecánica para aclarar el papel del tejido nervioso en procesos de sensibilización[58,59]. Además, Smoot et al[60] evaluaron recientemente diferentes grupos de mujeres con linfedema y dolor después del tratamiento del cáncer de mama, demostrando una mecanosensibilidad neuronal alterada en el miembro superior.

A pesar de todo lo anterior, la evidencia que apoya la participación del tejido nervioso en el proceso de sensibilización en pacientes de cáncer de mama todavía es insuficiente, aunque varios

estudios previos han utilizado los umbrales del dolor a la presión (UDP) como valoración de los nervios para evaluar la sensibilización central en diferentes condiciones, como en el síndrome del túnel carpiano[61], en el latigazo cervical asociado a trastorno[62], y en sujetos sanos[63].

La algometría de presión es una técnica con una alta fiabilidad que permite la evaluación de la sensibilidad de las estructuras somáticas profundas al dolor mecánico[64,65]. La grabación de múltiples UDP en una plantilla geométrica se puede utilizar para generar mapas de dolor a la presión y representar áreas del cuerpo hipo o hipersensibles[66]. Numerosos estudios han demostrado una relación entre las áreas más sensibles al dolor por presión y el desarrollo de hiperalgesia[67,68]. La región del hombro, y más concretamente la del trapecio superior e infraespinoso, se han estudiado mediante la generación de mapas del dolor en personas sanas con dolor músculoesquelético inducido experimentalmente y en pacientes con dolor musculoesquelético de cuello y hombro[69,70,71,72]. Curiosamente, la hipersensibilidad bilateral al dolor por presión apoya la participación de los mecanismos centrales de sensibilización en pacientes con dolor unilateral[72]. Sin embargo, hasta donde conocemos, los cambios bilaterales producidos en cuanto a la sensibilidad del dolor a la presión en la región del hombro incluyendo la zona dorsal (músculo trapecio superior) y la zona de la pared anterior del tórax (músculo pectoral mayor y deltoides) no han sido aún esclarecidos en las SCM.

La presencia de artralgia en las Mujeres Supervivientes de Cáncer de Mama

La terapia hormonal que se administra tras finalizar el tratamiento para el cáncer de mama puede estar asociada a artralgia debilitante en algunas de las pacientes. De hecho, la artralgia es considerada una de las causas más fecuentes que reducen la adherencia a la terapia hormonal en pacientes con cáncer de mama[73,74,75]. La incidencia real de artralgias o de síntomas músculoesqueléticos en las SCM que usan la terapia hormonal no es del todo conocida, aunque estos síntomas han sido estimados entre el 5-50%[76,77]. Este problema aparece con más frecuencia en las pacientes usuarias de inhibidores de aromatasa (IA), que en aquellas que toman tamoxifeno[78,79,80]. Sin embargo, estudios previos han publicado que la artralgia es un síntoma debilitante continuamente referenciado por una pequeña, pero significativa proporción de usuarias de tamoxifeno[81] con un perfil similar al del exemestano (tercera generación de IA)[82].

La obesidad[80] y la fatiga relacionada con el cáncer[83] también han sido asociadas a un aumento de la incidencia del dolor muscular y las artralgias en estas pacientes. Entendemos la fatiga inducida por cáncer (FIC) como un estado de agotamiento físico, emocional y/o cognitivo, que incapacita para la realización de actividades cotidianas, mermando por tanto la calidad de vida. Tradicionalmente, la estrategia utilizada para combatir la FIC ha sido el descanso[84]. Sin embargo, de acuerdo con un estudio realizado por Schmitz et al[85], la actividad física muestra efectos beneficiosos en la prevención y en la reducción de la fatiga asociada con el cáncer; es más, hoy en día se sabe que la inactividad física es precisamente uno de los factores que se relacionan con la aparición de la fatiga. La disminución de la actividad conduce a la reducción de la masa muscular y de la capacidad cardiovascular, por tanto, a la pérdida de la condición física general, que a su vez, aumenta la fatiga[86,87,88]. Por otro lado, sabemos que el ejercicio terapéutico regular mejora el estado subyacente en personas que padecen gran variedad de enfermedades crónicas no transmisibles, entre ellas el cáncer[89]. Además se ha demostrado que las mejoras en la fuerza muscular también mejora el perfil lipídico sanguíneo, reduce la presión sanguínea en reposo/ejercicio, mejora la tolerancia a la glucosa y la sensibilidad a la insulina, aumenta el gasto energético y reduce potencialmente el porcentaje de grasa abdominal[90], siendo este último uno de los principales predictores de mortalidad en población oncológica[91].

Es cierto que los expertos han investigado con una amplia variedad de intervenciones, aunque no está claro que cualquiera de éstas haya tenido un efecto significativo en estos síntomas[79,92]. Un estudio con eletroacupuntura produjo mejoras en la fatiga, la ansiedad y la depresión en pacientes con cáncer de mama que sufrían artralgia asociada a la terapia hormonal[93]. Un programa de yoga ya demostró la eficacia para reducir el dolor, y mejorar el equilibrio y la flexibilidad en SCM que sufren artralgia[94]. Y una intervención con un programa de ejercicios, redujo el dolor articular y los síntomas depresivos en pacientes con cáncer de mama[95].

El ejercicio acuático es una modalidad popular no farmacológica utilizada para el tratamiento de una gran variedad de afecciones, incluyendo el dolor músculoesquelético[96]. Las propiedades analgésicas de la hidroterapia pueden ser reguladas por la flotabilidad, que disminuye significativamente la carga de peso y el estrés que soportan las articulaciones, huesos y músculos[97]. Los ensayos clínicos han establecido que los pacientes con diferentes condiciones, como pueden ser fibromialgia[98], dolor asociado a la esclerosis múltiple[99], artritis reumatoide[100] o la osteoartritis[101],

tienen menos dolor cuando se utiliza la hidroterapia como tratamiento analgésico. Se han utilizado diferentes recursos, como la piscina de agua profunda en pacientes con dolor lumbar[102], pero otras posibilidades, como la piscina con el agua a la altura del pecho no habían sido exploradas anteriormente.

Hasta el momento, no conocemos la existencia de estudios previos que analicen la eficacia de la hidroterapia para mejorar los UDP, la composición corporal y la fatiga relacionada con el cáncer, en las SCM que padecen artralgia asociada a la terapia hormonal.

O

OBJETIVOS

AIMS

OBJETIVOS

Generales

Describir el tono vagal y el dolor musculoesquelético y neuropático en mujeres supervivientes de cáncer de mama.

Evaluar la efectividad de un programa de fisioterapia acuática sobre el dolor articular asociado a la hormonoterapia en mujeres supervivientes de cáncer de mama.

Específicos

Analizar la variabilidad de la frecuencia cardíaca en mujeres sanas y en mujeres supervivientes de cáncer de mama durante el primer año después de finalizar el tratamiento coadyuvante. **(Artículo I)**

Estudiar el dolor neuropático mediante tests de neurodinamia, y la presencia de hipersensibilidad generalizada a la presión mediante algometría sobre los troncos nerviosos de las extremidades superiores, en mujeres sanas y en mujeres supervivientes de cáncer de mama. **(Artículo II)**

Describir y localizar el dolor musculoesquelético mediante la determinación de los puntos más sensibles a la presión en mapas topográficos de la región frontal y dorsal del hombro y zonas de la mama en mujeres sanas y en mujeres supervivientes de cáncer de mama**. (Artículo III)**

Investigar el impacto de un programa de ejercicio acuático, de 8 semanas de duración, sobre los umbrales del dolor a la presión, la fatiga relacionada con el cáncer y la circunferencia de la cintura en mujeres supervivientes de cáncer de mama que sufren artralgias asociadas a la terapia hormonal. **(Artículo IV)**

AIMS

Overall

To describe the vagal tone and musculoskeletal and neuropathic pain in women breast cancer survivors.

To evaluate the effectiveness of an aquatic physiotherapy program on hormone therapy-associated arthralgia in breast cancer survivors.

Specifics

To analyze the heart rate variability in breast cancer survivors during the first year after completion of adjuvant treatment and healthy women. **(Paper I)**

To describe the neuropathic pain through study by neurodynamic tests, and the presence of widespread pressure hypersensitivity through algometry over the nerve trunks of the upper limbs, in healthy women and breast cancer survivors. **(Paper II)**

To describe and locate musculoskeletal pain by determining the most sensitive points to the pressure on topographic maps of the neck, front and back shoulder region and areas of the breast in healthy women and breast cancer survivors. **(Paper III)**

To investigate the impact of an aquatic phsiotherapy program of eight weeks, on pressure pain thresholds, cancer-related fatigue and waist circumference in breast cancer survivors suffering hormone therapy-associated arthralgia**. (Paper IV)**

M

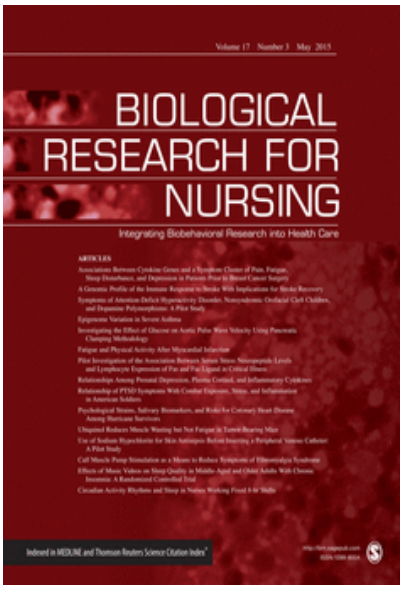
METODOLOGÍA
METHODOLOGY

PAPER	STUDY DESIGN	PARTICIPANTS	INTERVENTION	MAIN VARIABLES STUDIED	METHODS
I. Heart Rate Variability in Breast Cancer Survivors After the First Year of Treatments: A Case-Controlled Study	Cross-sectional study (case-control)	22 BCS 22 Healthy women (control)	Not applicable	Resting Heart Rate RHR Time domain: SDNN RMSSD HRV index Frequency domain: LF HF LF/HF ratio	Holter monitor NH300 software IBM-SPSS software.
II. Nerve Pressure Pain Hypersensitivity and Upper Limb Mechanosensitivity in Breast Cancer Survivors: A Case-Control Study	Cross-sectional study (case-control)	22 BCS 22 Healthy women (control)	Not applicable	Spontaneous neck and shoulder/axillary pain. PPT index (peripheral nerve trunks of the median, radial and ulnar nerves, and tibialis anterior muscle). ULNTs (median, radial and ulnar nerves). ROM (shoulder and elbow).	11-point numerical point rate scale. Bilaterally explored with electronic algometer (applied at approximate rate of 30 kPa/second by a 1 cm2 probe). Bilaterally manual examination. Standard goniometer.
III. Pressure Pain Sensitivity Maps of the Neck-Shoulder Region in Breast Cancer Survivors	Cross-sectional study (case-control)	22 BCS 22 Healthy women (control)	Not applicable	Spontaneous neck and shoulder pain. PPT index (15 points over upper trapezius muscle, 6 points over anterior deltoid muscle, 6 points over pectoralis major muscle, and 1 point over tibialis anterior muscle).	11-point numerical point rate scale. Bilaterally explored with electronic algometer (applied at approximate rate of 30 kPa/second by a 1 cm2 probe).
IV. Aquatic Exercise in a Chest-High Pool for Hormone Therapy-Induced Arthralgia in Breast Cancer Survivors: A Pragmatic Controlled Trial	Pragmatic parallel group controlled trial	40 BCS Experimental group (n=20) Control group (n=20)	8 weeks hydrotherapy program: aquatic exercise and physical recovery procedures, 3 times/week (experimental group) Usual care (control group)	PPT index (C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal, and tibialis anterior muscle). Fatigue Height Body mass index Waist circumference	Bilaterally explored with electronic algometer (applied at approximate rate of 30 kPa/second by a 1 cm^2 probe). Piper Fatigue Scale Stadiometer Kg m-2 Tape measure

R&D

RESULTADOS Y DISCUSIÓN

RESULTS AND DISCUSSION



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Heart Rate Variability in Breast Cancer Survivors After the First Year of Treatments: A Case-Controlled Study

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Abstract

The same aggressive treatments that have led to a reduction in the breast cancer may also have adverse effects on cardiac autonomic balance. The objective of this study was to compare heart rate variability (HRV) between breast cancer survivors in the first year posttreatment and healthy women, controlling for known confounders. This descriptive case-controlled study included 22 breast cancer survivors and 22 healthy age- and sex-matched controls. Short-term HRV was measured using an accepted methodology to assess the cardiac autonomic balance. One-way analysis of covariance results revealed that heart rate was significantly higher ($F = 15.86$, $p < .001$) and the standard deviation of normal-to-normal (NN) interval ($F = 19.93$, $p = .001$), square root of mean squared differences of successive NN intervals ($F = 18.72$, $p = .001$), HRV index ($F = 5.44$, $p = .025$), and high-frequency ($F = 5.77$, $p = .03$) values were significantly lower in the breast cancer survivors than in the matched controls. The principal finding of the presence of a cardiovascular imbalance in breast cancer survivors in comparison to healthy age-matched controls suggests that HRV study could be a clinically useful tool to detect cardiovascular disease in early-stage breast cancer survivors.

Keywords

breast cancer survivors, heart rate variability, autonomic nervous system

Breast cancer is the most frequent cancer among women and the second leading cause of cancer death after lung cancer in more developed countries (Ferlay et al., 2013). There has been an appreciable reduction in the breast cancer mortality rate over the past two decades, especially among women younger than 50 years of age (3.1% per year), attributable to improvements in early detection and treatment (Desantis, Ma, Bryan, & Jemal, 2014).

However, the same aggressive and prolonged therapies (Desantis et al., 2014) that have reduced the breast cancer mortality rate are also associated with adverse effects, including the impairment of cardiopulmonary functions (Scott et al., 2014). Anthracyclines, which are widely used in breast cancer treatment, have permanent cardiotoxic effects, anti-HER 2 drugs are responsible for reversible transient cardiac dysfunction, and drugs used in hormonal therapy alter lipid metabolism. Moreover, combinations of these chemotherapeutics can increase their cardiotoxic effects (Ades et al., 2014). Radiotherapy can also increase the risk of heart disease (Darby et al., 2013). The cardiotoxic effects of oncologic treatments may affect vagal activity and therefore influence cardiac autonomic balance (Ades et al., 2014; Darby et al., 2013).

Long-term autonomic imbalance is associated with an increased risk of cardiovascular disease and mortality (Thayer & Lane, 2007). There appears to be a bidirectional relationship between autonomic imbalance and cancer. Psychological and behavioral factors (e.g., stress, chronic depression, or lack of social support) can influence the incidence and progression of cancer (Armaiz-Pena, Cole, Lutgendorf, & Sood, 2013). Scott et al. (2014) recently reported that signals from tumor cells are transmitted via humoral and nervous pathways to the brain, which may therefore modify the neuroendocrine–immune system to regulate tumor growth in peripheral tissues. Conversely, autonomic dysfunction is common in many types of cancer and leads to increased sympathetic and decreased vagal tone in the heart (Jones et al., 2012). The vagal-nerve activity involved in sinus node function modulates key

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mechanisms in the development and progression of cancer (oxidative stress, DNA cell damage, inflammatory reaction, and excessive response of the sympathetic nervous system). De Couck, Mravec, and Gidron (2012) found that appropriate vagal activity favors a better prognosis in breast cancer patients.

Heart rate variability (HRV) is an important noninvasive index of vagal-nerve response and a potential stress marker (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). It may also be a useful test for autonomic imbalance (Guo, Palmer, Strasser, Yusuf, & Bruera, 2013). The index represents the time differences between beat-to-beat intervals, synonymous with RR variability (RR interval in the electrocardiogram [ECG]). Analysis of the time differences between successive heartbeats can be accomplished with reference to time (time-domain analysis) or frequency (frequency-domain analysis; Task Force, 1996). The parasympathetic and sympathetic nervous systems, which are primarily responsible for changes in the interbeat interval, modify the heart rate and can be quantified by using HRV time- and frequency-domain parameters (Masters, Stevenson, & Schaal, 2004).

According to the American College of Cardiology and American Heart Association, oncology patients who have received chemotherapy, especially with anthracyclines, high doses of cyclophosphamides or trastuzumab, represent a high-risk group (Stage A) for heart failure (Hunt et al., 2009). Research has shown that coadjuvant cancer treatments reduce HRV values after surgery (Hansen, Rosenberg, & Gögenur, 2013), radiotherapy (Hoca, Yildiz, & Ozyigit, 2012), and chemotherapy (Poręba et al., 2014).

A correct prognosis is crucial in cancer treatment, and routine HRV tests may be useful for clinical decision making and management of the disease (Chiang, Kuo, Fu, & Koo, 2013). HRV is strongly correlated with vagal-nerve activity and is mainly governed by efferent cardiac vagal-nerve activity, which it reflects (Kuo, Lai, Huang, & Yang, 2005). Low vagal-nerve activity in cancer patients can act as a risk factor, whereas high activity plays a protective role (De Couck, Mravec, & Gidron, 2012). Thus, researchers have observed lower HRV levels in more advanced stages of various cancers (De Couck & Gidron, 2013; Guo et al., 2013; Kim et al., 2010; Wang, Wu, Huang, Kou, & Hseu, 2013).

Limited information is available on the autonomic balance during the early survivorship phase in breast cancer patients. To our knowledge, no other controlled studies have compared HRV values between breast cancer survivors in the first year posttreatment and comparable healthy women. We hypothesized that HRV levels would be lower in breast cancer survivors during the first year posttreatment than in healthy women.

Materials and Methods

Participants

This descriptive case-controlled study included 22 breast cancer survivors recruited from a department of Oncology in a hospital in Granada, Spain, and 22 healthy age- and sex-matched controls recruited from the general community. Inclusion criteria were a primary diagnosis of breast cancer (Grades I–IIIa), age between 18 and 65 years, and completion of post-primary cancer treatment (surgery, chemotherapy, and/or radiotherapy) between 6 months and 1 year earlier. Exclusion criteria were presence of metastasis and/or active cancer, history of cardiovascular disease, and receipt of medication known to alter vagal-nerve activity. The ethics committee of the hospital approved the study. We contacted patients and made appointments with those expressing an interest in study participation to sign their informed consent, complete their medical history, undergo a physical examination, and complete a questionnaire on their age, surgical side, comorbidities, socio-educational level, marital status, and previous oncologic treatments.

HRV Measurements

We measured short-term HRV using an accepted method in order to assess the cardiovascular balance (Wang et al., 2013). We asked participants to lie in a supine position for 10 min of rest with no external stimulation in a quiet room with a temperature of 22–25 °C. ECG signals were then acquired using a Holter monitor (Norav Holter DL 800, Braemar, Brunsville, MN) for 5 min, using a modified lead II channel system. HRV was calculated from ECG records as the time interval between consecutive heartbeats (RR interval). In the time domain, we analyzed the standard deviation of the average normal-to-normal (NN) interval (SDNN), the square root of the mean squared differences of successive NN intervals (RMSSD), and the number of all NN intervals divided by the maximum of all NN intervals (HRV index). The main spectral components analyzed in the frequency domain were the low-frequency (LF) band (0.04–0.15 Hz), as a measure of sympathetic and parasympathetic activities; high-frequency (HF) band (0.15–0.40 Hz), associated with vagal–parasympathetic activity; and the LF/HF ratio, indicating the sympathovagal balance. We followed the recommendations of the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology (Task Force, 1996). The spectral analysis was performed with NH300 software (Norav, version 2.70) using fast Fourier transform algorithms. The sampling rate was 256 samples per second and the frequency filter was set at 0.05 to 60 Hz. Because of the low sampling rate, the software used an interpolation algorithm to improve R-peak detection.

Statistical Analysis

Results were expressed as means with standard deviation for continuous variables and as percentages for categorical variables with 95% confidence interval. Parametric and nonparametric tests were applied after applying the Kolmogorov–Smirnov test to check the normal distribution of the data. When necessary, data were log transformed to achieve homogeneity of variance. One-way analysis of covariance (ANCOVA) was performed with group (health and cancer) as between-subject variables and heart rate, SDNN, RMSSD, HRV index, HF,

Table 1. Participant Characteristics by Study Group.

Variable	Healthy controls ($n = 22$)	Breast cancer ($n = 22$)	p value
Age[a] (years), *mean* + *SD* (range)	50.36 ± 7.68 (37–67)	50.23 ± 7.82 (37–66)	.931
Marital status[b] (%)			.639
Single	9.1	13.6	
Married	72.7	77.3	
Divorced	18.2	9.1	
Educational level[b] (%)			.211
Primary studies	4.5	18.2	
Secondary studies	45.5	22.7	
High school	50	54.5	
Occupational status[c] (%)			.021*
Homemaker	4.5	13.6	
Employed	86.4	31.8	
Sick leave	0	36.4	
Not working due to the disease	0	18.2	
Retired	9.1	0	
Smoking status[c] (%)			.05*
Nonsmoker	59.1	40.9	
Smoker	31.8	9.1	
Ex-smoker	9.1	50	
Alcohol status[b] (%)			.501
No consumption	36.4	18.2	
Consume monthly	22.7	36.4	
Consume weekly	36.4	36.4	
Consume daily	4.5	9.1	
Menopausal status[b] (%)			.073
Premenopausal	59.1	31.8	
Postmenopausal	40.9	68.2	
Weight (kg)[a], *mean* + *SD* (range)	63.22 ± 8.30 (50.2–84.90)	65.4 ± 6.98 (50.7–84.1)	.280
Height (cm)[d], *mean* + *SD* (range)	162.30 ± 5.4 (153–176)	158.9 ± 5.05 (149–167)	.057
BMI (kg/m^2)[d], *mean* + *SD* (range)	24.07 ± 3.40 (20.10–34)	25.95 ± 2.92 (21.4–32)	.024*

Note. BMI = body mass index.
[a]Student *t*-test, [b]χ^2 test, [c]Mann–Whitney *U* test, and [d]Wilcoxon test were performed for comparisons between groups.
*$p < .05$.

LF, and HF/LF ratio as within-subject variables, considering the following covariates: age, educational level, marital status, occupation, smoking habit, alcohol use, menopausal status, height, weight, and body mass index (BMI). IBM-SPSS 21.0 was used for the data analyses, and $p < .05$ was considered statistically significant.

Results

Demographic and Clinical Data

The study sample comprised 44 Caucasian women with a *mean* (*SD*) age of 50.30 (7.66) years. More than half (55%) of the 22 breast cancer survivors were not working due to incapacity or sick leave, which differed significantly from the group of healthy women. The mean BMI was higher in the cancer survivors than in the healthy women (25.95 vs. 24.07 kg/m^2; $p = .024$). The two groups also differed significantly in smoking status (see Table 1). We found no significant intergroup differences in the other variables (Table 1).

Among the patients, the mean time since diagnosis was 12.5 months, Stage II disease was present in 54.6 of cases, the surgery type was quadrantectomy in 63.6% of cases, both radiation and chemotherapy postsurgery were received as adjuvant treatment in 77.3% of cases, the estrogen receptor antagonist tamoxifen was administered in 22.7% of cases, and the aromatase inhibitor anastrozole in 40.9%. These and other clinical characteristics for the women with cancer are shown in Table 2.

HRV Analysis

ANCOVA results revealed significant differences in time and frequency domains between the breast cancer and healthy groups. In addition, heart rate values were significantly higher ($F = 15.86$, $p < .001$) in the breast cancer survivors than in the healthy controls.

Time domain measurements. SDNN ($F = 19.93$, $p < .001$), RMSSD ($F = 18.72$, $p < .001$) and HRV index ($F = 5.44$, $p = .025$) values were significantly lower in the breast cancer survivors than in the matched controls (Table 3). The covariates studied showed no influence from the type of treatment.

Table 2. Clinical Characteristics of Participating Breast Cancer Patients.

Variable	Cancer patients ($n = 22$)
Time since diagnosis (months), *mean* + *SD*	12.5 ± 6.04
Tumor stage (%)	
I	22.7
II	54.6
IIIa	22.7
Type of medical treatment (%)	
Radiotherapy	13.6
Chemotherapy	9.1
Radiotherapy + chemotherapy	77.3
Type of surgery (%)	
Quadrantectomy	63.6
Unilateral mastectomy	36.4
Hormonal therapy (%)	
Tamoxifen	22.7
Aromatase inhibitor	40.9
None	36.4
Herzeptin (%)	18.8

Frequency domain measurements. In the frequency domain, the HF parameter was significantly lower ($F = 5.77$, $p = .03$) and the LF and LF/HF ratio were nonsignificantly higher in the breast cancer survivors than in the healthy controls (Table 3). The covariates studied showed no influence in this analysis.

Discussion

The principal finding of this study was the presence of a cardiovascular imbalance in breast cancer survivors in comparison to healthy age-matched controls, as evidenced by a higher resting heart rate and lower values for HRV time domains (SDNN, RMSSD, and HRV index) and the high band (HF) of the HRV frequency domain. Although we observed higher values in the breast cancer survivors for the other HRV frequency components studied (LF band and LF/HF ratio), the differences did not reach significant levels. This cardiovascular imbalance, reflected by a parasympathetic nervous system withdrawal and sympathetic nervous system increase, is generally considered arrhythmogenic (Masters & Stevenson, 2003), may have a complex origin, and has been associated with multiple factors, including the type of oncologic treatment, cancer-related symptoms during survivorship phase (e.g., pain, fatigue, anxiety, etc.), and the presence of comorbidities. Elucidation of the relative influence of these factors is beyond the scope of this study but warrants further research.

These results confirm previous observations on the reduced HRV and low cardiac vagal tone (Task Force, 1996) in breast cancer survivors during the first year after treatment. A reduced HRV has been associated with an increased risk of cardiovascular disease and mortality in noncancer populations (Frodl & O'Keane, 2013), elevated self-reported stress (Chandola, Heraclides, & Kumari, 2010), and increased arterial stiffness in people with Type I diabetes (Jaiswal et al., 2013).

A major drawback of research in which HRV is the variable of interest is the lack of a generally accepted HRV cutoff point that defines inadequate cardiovascular balance. Our result of a mean RMSSD of 28.8 ms among the breast cancer patients in this study does not differ significantly from published findings in 113 prostate cancer patients after diagnosis (32 ms; $p = .533$; De Couck, van Brummelen, Schallier, De Greve, & Gidron, 2013), in 84 patients aged ≤50 years with early-stage breast cancer at ≥5 months after radiotherapy or chemotherapy (29 ms; $p = .97$; Crosswell, Lockwood, Ganz, & Bower, 2014), and in women with breast cancer at 14 days after lumpectomy (26 ms; $p = .6$; Hansen et al., 2013). With regard to the frequency domain, the expected reduction in the HF band that we found in our study is in line with previous report on the effects of cancer treatment on this domain (Hoca et al., 2012).

One finding of interest that has come out of previous studies is that HRV values were higher in the early survivorship phase than in advanced cancer (colon, prostate, pancreatic, ovarian, and non-small cell lung; De Couck & Gidron, 2013; De Couck et al., 2013). Guo and colleagues (2013) found that an SDNN value < 40 ms predicted moderate/severe autonomic dysfunction in advanced lung, gastrointestinal, sarcoma, and genitourinary cancer patients, while others reported that an SDNN < 21.3 ms in brain metastasis (Wang et al., 2013) and <10 ms in terminal-stage cancer (Kim et al., 2010) predicted poor survival. Further research is warranted on HRV in cancer patients to establish its potential role in clinical follow-up.

In this novel study, we used a case-controlled design, which is frequently used in studies with oncology patient (Fernández-Lao et al., 2010; Sánchez-Jiménez et al., 2014), to analyze vagal-nerve activity while considering different confounder variables. However, we should acknowledge some limitations. First, HRV measurements may only partly represent vagal-nerve activity while primarily reflecting cardiac vagal activity, although there is evidence of a strong correlation between HRV and vagal activity (Kuo et al., 2005). Second, we measured HRV with an ECG over a 5-min period rather than using 24-hr monitoring. However, the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) recommends this short-term HRV method and it is the most widely used approach in cancer patients (Wang et al., 2013). Third, we did not control for the respiratory rate, whose influence is currently under debate given that consciously controlled breathing may affect HF values by inhibiting cardiac parasympathetic-nerve activity (Sasaki & Maruyama, 2014). Finally, prospective multicenter studies with large samples are required to establish reference HRV and cutoff points in cancer survivors and determine the influence of different oncologic treatments on HRV parameters, with the aim of testing HRV's usefulness in monitoring the cardiac health of cancer patients.

If further study confirms that HRV is a clinically useful tool to detect cardiovascular disease and predict prognosis in early-stage breast cancer survivors, various nonpharmacological therapies that improve altered cardiovascular balance may then be available for use among these patients. These therapies

Table 3. Comparison of the Dependent Variables of Heart Rate Variability (HRV) Between the Study Groups.

Variable	Healthy controls ($n = 22$) *Mean* + *SD* (95% CI)	Breast cancer ($n = 22$) *Mean* + *SD* (95% CI)	*p* value
RHR (bpm)[a]	68.27 ± 7.6 [64.90, 71.64]	79.29 ± 11.19 [75.45, 86.77]	.000*
Time domain			
SDNN (ms)[a]	62.35 ±1 8.21 [48.32, 80.19]	39.10 ± 16.28 [11.47, 74.10	.000*
RMSSD (ms)[a]	58.65 ± 22.17 [43.36–72.58]	28.82 ± 23.52 [14.96–29.43]	.000*
HRV index[a]	7.49 ± 2.03 [6.59, 8.40]	6.07 ± 2.02 [5.17, 6.96]	.025*
Frequency domain			
LF (ms^2)[b]	144.96 ± 89.4 [105.32, 184.60]	169.05 ± 79.71 [133.71, 204.39]	.351
HF (ms^2)[b]	193.36 ± 92.7 [152.26, 234.47]	136 ± 62.80 [108.15, 163.85]	.03*
LF/HF ratio[b]	1.11 ± 1.21 [0.57, 1.65]	1.4 ± 0.82 [1.03, 1.76]	.363

Note. CI = confidence interval; RHR = resting heart rate; SDNN = standard deviation of the normal-to-normal interval; RMSSD = square root of the mean squared differences of successive NN intervals; LF = low frequency; HF = high frequency.
[a]Wilcoxon and [b]ANCOVA tests were performed for comparison of different variables.
*$p < .05$.

include manual therapy (Fernández-Lao et al., 2012), reiki (Díaz-Rodríguez et al., 2011), physical exercise (Niederer et al., 2013), relaxation exercises (e.g., guided imagery; Lee, Kim, & Yu, 2013), meditation (Krygier et al., 2013), yoga (Mackenzie et al., 2014), and controlled breathing (Howorka et al., 2013). This type of approach could be combined with anticancer treatments to correct the autonomic nervous system balance and consequently improve the outcomes in breast cancer survivors.

Author Contribution

EC-M contributed to design, data acquisition, data analysis, interpretation; critically revised the manuscript; gave final approval; and agrees to be held accountable for all aspects of work, ensuring integrity and accuracy. CF-L contributed to design, data acquisition, data analysis, interpretation; critically revised the manuscript; gave final approval; and agrees to be held accountable for all aspects of work, ensuring integrity and accuracy. NG-C contributed to design, data acquisition, data analysis, interpretation; critically revised the manuscript; gave final approval; and agrees to be held accountable for all aspects of work, ensuring integrity and accuracy. IC-V contributed to design, data acquisition, data analysis, interpretation; critically revised the manuscript; gave final approval; and agrees to be held accountable for all aspects of work, ensuring integrity and accuracy. MA-M contributed to conception, design, interpretation; drafted and critically revised the manuscript; gave final approval; and agrees to be held accountable for all aspects of work, ensuring integrity and accuracy. LD-R contributed to conception, design, interpretation; drafted and critically revised the manuscript; gave final approval; and agrees to be held accountable for all aspects of work, ensuring integrity and accuracy.

Declaration of Conflicting Interests

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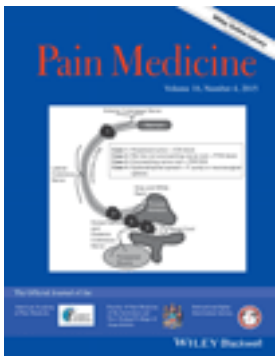
Pain Medicine



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CANCER PAIN & PALLIATIVE CARE SECTION

Original Research Article

Nerve Pressure Pain Hypersensitivity and Upper Limb Mechanosensitivity in Breast Cancer Survivors: A Case–Control Study

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Abstract

Objective. This study aims to investigate the presence of bilateral pressure pain hypersensitivity in arm trunk nerves and upper limb mechanosensitivity in breast cancer patients with neck-shoulder pain after medical treatments.

Methods. Twenty-two breast cancer survivors (mean age 49.05 ± 7.8 years) and matched healthy controls (mean age 50.76 ± 7.6 years) participated in the study. Neck and shoulder pain was evaluated using an 11-point numerical point rating scale. Pressure pain thresholds (PPTs) were bilaterally assessed over the median, radial, and ulnar nerve trunks and tibialis muscle, and the neurodynamics of the upper limb by neural tolerance to movement was evaluated in the median, radial, and ulnar nerves.

Results. Thirteen (59.1%) patients reported spontaneous neck pain, and 16 (72.7%) patients showed spontaneous shoulder/axillary pain. Analysis of variance revealed that breast cancer survivors showed significant between-group but not between-side differences over the median nerve trunk (group: $P = < 0.001$; side: $P = 0.146$), radial nerve trunk (group: $P = < 0.001$; side: $P = 0.300$), ulnar nerve trunk (group: $P = < 0.001$; side: $P = 0.744$), and tibialis anterior muscle (group: $P = < 0.001$; side: $P = 0.118$). The patients also showed statistically significant differences in range of motion (ROM) between groups and between sides in $ULNT1_{MEDIAN}$ (group: $P = < 0.001$; side: $P = < 0.001$) and $ULNT_{ULNAR}$ (group: $P = 0.009$; side: $P = 0.002$). The analysis did not show statistically significant differences in ROM between groups, but there was a statistical significance between sides for $ULNT_{RADIAL}$ (group: $P = 0.081$; side: $P = 0.046$).

Conclusions. Breast cancer survivors present bilateral and widespread neural hypersensitivity, as they did in muscular tissue in previous studies. Breast cancer survivors demonstrate a reduction in ROM during ULNTs in the affected side.

Key Words. Breast Cancer; Pain; Sensitization; Nerves; Pressure Pain Threshold

Introduction

Breast cancer is the most frequently diagnosed type of this disease and is the leading cause of cancer death among women worldwide [1]; its incidence has risen in recent years [2], with this upward trend being more important in Spain than in other European countries [3]. Screening programs and advances in diagnosis and therapeutic approaches have resulted in a survivorship during the last years of approximately 70% at 5 years after diagnosis [4], which makes breast cancer a chronic condition with important consequences.

A great number of survivors have upper extremity comorbidities such as pain, neuropathy, and mobility reduction [5], with an important relationship with a higher self-perceived disability and a lower quality of life [5,6]. The combination of axillary dissection and radiotherapy as the standard treatment option is related to the occurrence of

important side effects in breast cancer patients, including pain, arm swelling, and shoulder stiffness [7]. Indeed, the prevalence of neck and shoulder pain in breast cancer patients is 47% [8]. However, the pathogenic mechanisms of this condition are complex and may be related to patient characteristics (age, sex, and genetics), surgical technique, and adjuvant therapy.

The importance and chronicity of such symptoms suggest that the mechanism of pain should be studied in addition to the specific structural pathology [9]. Moreover, previous studies have described widespread pressure pain muscle hypersensitivity as a sign of a central sensitization mechanism in cancer survivors [10,11] and especially in breast cancer patients [10]. Postmastectomy pain is attributed to damage of peripheral nerves during surgery [12]. Evidence supporting the participation of nerve tissue in the sensitization process in breast cancer patients is postulated but still insufficient, even though several previous studies have used pressure pain threshold (PPT) assessment within nerves to evaluate central sensitization in different conditions, such as carpal tunnel syndrome [13], whiplash-associated disorder [14], and healthy subjects [15].

The contribution of medical oncology treatment to nerve tissue damage is well known. On the one hand, radiotherapy can cause brachial plexopathy [16,17], and this radiation-induced brachial plexopathy may be due to nerve damage or the compression of nerve fibers via fibrosis of the axillary and supraclavicular connective tissue [16]. This nerve damage has been associated with sensorimotor and functional deficits [18]. On the other hand, chemotherapy can induce peripheral neuropathy [19,20] and increases the risk of brachial plexus damage. Different factors such as the disruption of axoplasmic transport or axonal degeneration or damage to sensory nerve cells are related to the pathophysiology of this phenomenon [21], which can make the nerves more susceptible to chronic compression [22]. We hypothesized that this nerve damage could contribute to pain sensitization processes in breast cancer survivors.

Tests based on mechanical stimulation have been used to clarify the role of nerve tissue in sensitization processes [23,24]. Brachial provocation tests have been used to clarify the mechanosensitivity of nerves in arm whiplash-associated disorder [9,25], carpal tunner syndrome [26], or lateral epicondylalgia [27]. In addition, Smoot et al. [28] recently assessed different groups of women with lymphedema and pain after breast cancer treatment and demonstrated an altered neural mechanosensitivity in the upper limb. However, the design of this study, using the non-affected side as a control, did not afford knowledge of the implication of central sensitization on the mechanosensitivity process.

As the mechanism involving the role of nerve damage in the central sensitization process in breast cancer survivors remains unclear, the aim of this study was to investigate bilateral pressure pain hypersensitivity in arm trunk nerves and upper limb mechanosensitivity in breast cancer patients with neck–shoulder pain after treatment. We hypothesized that breast cancer survivors have bilateral and widespread nervous hypersensitivity and greater upper limb mechanosensitivity compared with matched healthy controls.

Materials and Methods

Participants

Twenty-two breast cancer survivors recruited from the Department of Oncology at the Virgen de las Nieves Hospital in Granada (Spain) participated in this observational case–control study. To be eligible for this study, the participants had to meet the following inclusion criteria: 1) first time with a primary diagnosis of breast cancer (grades I–IIIA); 2) women who had received a lumpectomy, quadrantectomy, or mastectomy; 3) women who had received surgery at least 6 months prior without breast cancer recurrence; 4) women who had completed adjuvant therapy (i.e., radiation and cytotoxic chemotherapy) at least 3 months before the study; 5) adults at least 18 years of age; and 6) neck and/or shoulder/axillary pain that began after breast cancer treatment. The exclusion criteria included: 1) bilateral breast cancer; 2) breast surgery for cosmetic reasons or prophylactic mastectomy; 3) other medical conditions (e.g., arthritis and fibromyalgia syndrome); 4) the presence of lymphedema; and 5) recurrent cancer.

The control group was recruited from volunteers who responded to an announcement from the university and were matched by age with the breast cancer survivor group. These subjects were excluded if they had had any prior chronic pain or trauma in the cervical spine, head, or upper limb. Ethical clearance for the study was obtained from the University Ethics Committee, following the Helsinki Declaration. All participants in this study signed an informed consent form before their inclusion.

The sample size calculation and power determination were performed by detecting, at least, significant clinical differences of 20% in PPT levels between the groups, with an alpha level of 0.05, a desired power of 80%, and an estimated interindividual coefficient of variation of PPT measures of 20%. This procedure was carried out using software (Tamaño de la muestra 1.1, Pontificia Universidad Javeriana, Unidad de Epidemiología Clínica, Bogotá, Spain); a sample of at least 16 subjects per group was calculated.

Measurements

Pain Intensity

We used an 11-point numerical point rating scale [29] (0 = no pain; 10 = maximum pain) to assess the intensity of spontaneous neck and shoulder/axillary pain. The patients did not take analgesics or muscle relaxants for 24 hours prior to the assessment.

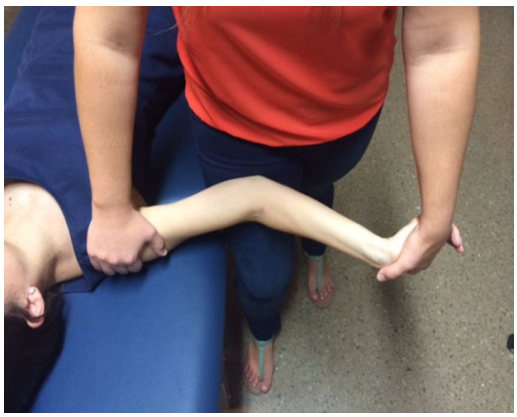

Figure 1 Upper limb neurodynamic test for median nerve.

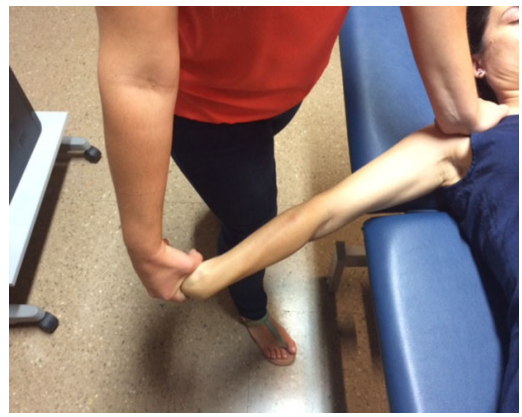

Figure 2 Upper limb neurodynamic test for radial nerve.

PPTs

PPTs were assessed bilaterally over the peripheral nerve trunks of the median, radial, and ulnar nerves. We identified the median nerve in the internal biceps groove, adjacent and medial to the tendon of the biceps muscle. The radial nerve was assessed when passing through the lateral intermuscular septum between the medial and lateral heads of the triceps muscle to enter the mid to lower third of the humerus bone. The ulnar nerve trunk was identified passing through the olecranon and the medial epicondyle [9]. The tibialis anterior muscle point was established as a distant site in the lower limb [10,30].

PPT is defined as the minimal amount of pressure for which a sensation of pressure first changes to pain [31]. An electronic algometer (Somedic AB, Farsta, Sweden) was used to measure PPT levels. The pressure was applied at an approximate rate of 30 kPa/s by a 1 cm^2 probe. The subjects were instructed to press a switch immediately when the sensation changed from pressure to pain. The mean of three trials was calculated for the main analysis. A 30-second resting period was provided between measurements at each point. This method of measuring PPT has been shown to exhibit high reliability {intraclass correlation coefficient = 0.91 (95% confidence interval [CI] 0.82–0.97)} [32].

Upper Limb Neurodynamic Tests (ULNTs)

Neurodynamics testing was used to assess neural tolerance to movement. ULNTs for the median ($ULNT1_{MEDIAN}$) (Figure 1), radial ($ULNT_{RADIAL}$) (Figure 2), and ulnar nerves ($ULNT_{ULNAR}$) (Figure 3) were performed according to the process described by Butler [33]. The patients were positioned in a supine position without a pillow under the head or knees and the legs uncrossed. The head was at a neutral rotation, and the hand of the untested arm rested on the side. All the ULNTs were performed bilaterally with a standardized sequence until the end of range or until the symptoms were reproduced. Prior to performing the tests, the patients were instructed to communicate the onset of any sensation such as pain or stretch in the areas of the arm and neck. The subject's pain and other symptoms were respected during all of the tests. Every test was carried out on the unaffected side for the first time, and the sensation was used as a reference for the affected arm. If the patient did not experience pain, we continued with the elbow extension or the shoulder abduction to the normal end of range. To measure shoulder and elbow range of motion (ROM) at the end of test performance, we used a standard goniometer based on a previously reported procedure [34]. The tests were stopped when the patient identified, at least partially, symptoms, the shoulder girdle attempted to elevate, or the examiner found muscular resistance to movement. A similar methodology has been described in studies of brachial plexus provocation tests [28,35].

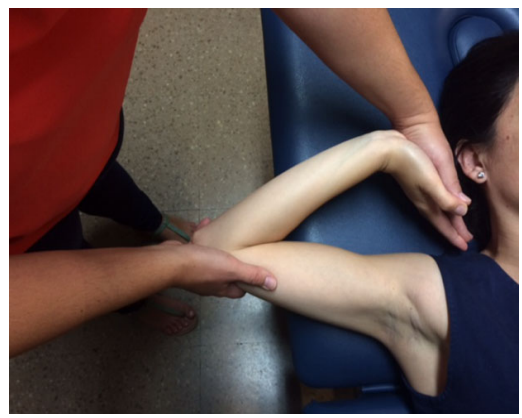

Figure 3 Upper limb neurodynamic test for ulnar nerve.

Statistical Analysis

The data were analyzed using IBM SPPS Statistics (20.0 version; IBM Corp., Armonk, NY, USA). The results are expressed as the mean, standard deviation (SD), or 95% CI. The Kolmogorov–Smirnov test was used to analyze the normal distribution of the variables ($P > 0.05$). As the PPT and ULNTs showed a normal distribution, we used parametric tests. To investigate the differences in PPT over each point (median, radial, ulnar nerves, and tibialis anterior muscle) and the differences in ROM during ULNTs, we used a two-way analysis of variance (ANOVA) with the side (affected/nonaffected for patients and dominant/nondominant for controls) as the within-patient factor and the group (patient and matched-control) as the between-patient factor. The statistical analysis was conducted at the 95% CI; $P < 0.05$ was considered statistically significant.

Results

Twenty-two women aged 31–63 years (mean ± SD 49.05 ± 7.8 years) who had received breast surgery as treatment for breast cancer and 22 healthy controls aged 37–67 years (mean ± SD 50.76 ± 7.6 years) participated in the study. Eleven (50%) patients had the right side affected, and the remaining 11 (50%) had the left side affected. At the time of the study, six (27.3%) patients were taking ibuprofen, four (18.2%) were taking paracetamol, two (9.1%) were taking metamizol, and one (4.5%) were taking tramadol. The principal descriptive results of the sample and differences between the groups are summarized in Table 1.

PPTs

The ANOVA revealed statistically significant differences in PPT levels between the groups but not between sides for the median nerve trunk (group: $F = 27.380$; $P = < 0.001$; side $F = 2.158$; $P = 0.146$), radial nerve trunk (group: $F = 25.88$; $P = < 0.001$; side: $F = 1.089$; $P = 0.300$), ulnar nerve trunk (group: $F = 30.789$; $P = < 0.001$; side: $F = 0.107$; $P = 0.744$), and tibialis anterior muscle (group: $F = 20.521$; $P = < 0.001$; side: $F = 2.522$; $P = 0.118$). The patients showed bilateral lower PPT levels compared with the healthy controls over each point assessed. A post hoc analysis showed that the PPTs over the affected median nerve (Bonferroni; $P = 0.001$), radial nerve (Bonferroni; $P = 0.008$), and tibialis anterior muscle (Bonferroni; $P = 0.031$) were significantly lower compared with the nonaffected side. Table 2 summarizes the PPT levels over each point assessed for both sides within each group.

ULNTs

The ANOVA analysis showed statistically significant differences in ROM between the groups and between sides for $ULNT1_{MEDIAN}$ (group: $F = 19.437$; $P = < 0.001$; side: $F = 27.33$; $P = < 0.001$) and $ULNT_{ULNAR}$ (group: $F = 7.047$; $P = 0.009$; side: $F = 10.535$; $P = 0.002$). In contrast, this analysis did not show statistically significant differences in ROM between the groups but was statistically significant between sides for $ULNT_{RADIAL}$ (group: $F = 3.120$; $P = 0.081$; side: $F = 4.107$; $P = 0.046$). The post hoc analysis revealed that the ROMs for $ULNT1_{MEDIAN}$ and $ULNT_{ULNAR}$ were significantly lower in the affected side compared with the nonaffected side (Bonferroni; $P < 0.001$). Table 3 shows the ROM from each ULNT assessed for the median, radial, and ulnar nerves.

Discussion

The principal findings of this study are the presence of widespread nervous hypersensitivity in breast cancer survivors and the presence of mechanosensitivity in the upper extremity, only in the affected side in breast cancer survivors with neck–shoulder pain compared with healthy controls.

In this study, we found bilaterally and widespread nervous hypersensitivity in breast cancer survivors compared with healthy controls, which were expressed as significantly decreased PPT levels over the median, radial, and ulnar nerve trunks. This finding supports the stated hypothesis regarding the generalized sensitization of neural tissue in these patients because PPT levels were lower in the affected extremity, in the nonaffected extremity, and in a distant area. All participants in the patient group showed spontaneous neck–shoulder pain, which could explain the initiation of central sensitization. Previous studies have found central sensitization in the same population [10,30] but had investigated pressure pain hypersensitivity only in muscular tissue. Therefore, the present work provides additional information of the responses to mechanical stimulation over peripheral nerve tissue. Sterling et al. [9] found similar results over peripheral nerve tissue in patients with neck pain after whiplash injury but did not find a significant interaction between sides in the experimental group. In several studies of this population, central and peripheral sensitization was found in the patient group, as assessed through PPTs in different nerve and muscular points [14,36]. One possible reason explaining our results is that chemotherapy can cause peripheral neuropathy [19,20] due to sensory axonal damage, with reduced amplitude of sensory nerve action potentials [37] and changes in afferent activity, leading to widespread pain sensitivity [38]. This neuropathy has been described as symmetric, distal, and length-dependent distribution [39]. It is also dose dependent and consists of sensory rather than motor symptoms [40].

Second, our results showed that breast cancer survivors demonstrate hyperalgesic responses to ULNTs, a clinical test of the mechanical provocation of peripheral nerve tissue. The patients showed mechanosensitivity in the upper extremity of the affected side compared with healthy controls, as demonstrated by a statistically significant reduced ROM in elbow extension and shoulder abduction during ULNTs for the median, radial, and ulnar nerves. Interestingly, these reductions were not significant in the nonaffected side, as occurred with regard to pressure hypersensitivity. In this respect, our results agree with

Table 1 Participant demographic and clinical characteristics

Variable	Patients with postmastectomy pain N = 22	Healthy control participants N = 22	*P* value
Age (years)	49.05 ± 7.847 (95% CI 45.57–52.52)	50.36 ± 7.681 (95% CI 46.96–53.77)	0.576
Weight (kg)	66.39 ± 10.604 (95% CI 61.693–71.097)	63.22 ± 8.303 (95% CI 59.541–66.904)	0.275
Height (cm)	162.0 ± 5.960 (95% CI 159.357–164.642)	162.30 ± 5.405 (95% CI 159.904–164.698)	0.861
Marital status, N (%)			0.108
Married	19 (86.4%)	16 (72.7%)	
Single	3 (13.6%)	2 (9.1%)	
Divorced	0	4 (18.2%)	
Widow	0	0	
Educational level, N (%)			0.213
Primary studies	5 (22.7%)	1 (4.5%)	
Secondary studies	8 (36.4%)	10 (45.5%)	
University studies	9 (40.9%)	11 (50.0%)	
Tobacco consumption			0.659
Nonsmoker	11 (50.0%)	13 (59.1%)	
Smoker	7 (31.8%)	7 (31.8%)	
Ex-smoker	4 (18.2%)	2 (9.1%)	
Alcohol consumption			0.746
No consumption	9 (40.9%)	8 (36.4%)	
Monthly	4 (18.2%)	5 (22.7%)	
Weekly	9 (40.9%)	8 (36.4%)	
Daily	0	1 (4.5%)	
Time from diagnosis (months)	26.41 ± 13.465 (95% CI 20.44–32.38)		
Time from surgery (months)	21.14 ± 14.301 (95% CI 14.80–27.48)		
Medical treatment			
Radiotherapy	2 (9.1%)		
Chemotherapy	0		
Radio + chemotherapy	20 (90,9%)		
Type of chemotherapy			
Epirubicin + ciclophosphamide (EC)	8 (36.4%)		
Taxotere (TXT)	2 (9.1%)		
EC + TXT	6 (27.3%)		
TXT + epirubicin	2 (9.1%)		
Docetaxel	2 (9.1%)		
No chemotherapy	2 (9.1%)		
Area of radiation			
Mammary gland	8 (36.4%)		
Mammary gland + axilla-supraclavicula area	7 (31.8%)		
Chest wall	3 (13.6%)		
Chest wall + axilla-supraclavicula area	4 (18.2%)		
Type of surgery			
Lumpectomy	8 (36.4%)		
Quadrantectomy	6 (27.3%)		
Unilateral mastectomy	8 (36.4%)		
Menopausal status			0.000*
Premenopause	1 (4.5%)	13 (59.1%)	
Postmenopause	21 (95.5%)	9 (40.9%)	

* Significant differences between groups (χ^2 test).
Values ± SD are expressed as mean (95% confidence interval) and absolute percentages.

Table 2 Pressure pain thresholds (kPa) in patients with postmastectomy pain and healthy controls

	Median nerve trunk	Radial nerve trunk	Ulnar nerve trunk	Tibialis anterior muscle
Patients with postmastectomy pain				
Affected	102.2 ± 52.7* (60.0–134.1)	124.7 ± 64.3* (83.3–170.4)	161.4 ± 94.8* (84.8–226.5)	181.3 ± 67.3* (132.3–226.8)
Nonaffected	135.8 ± 58.9* (82.6–163.9)	144.0 ± 60.3* (98.2–182.2)	167.4 ± 84.9* (118.7–208.4)	255.3 ± 104.3* (185.2–325.4)
Healthy control participants				
Dominant	186.6 ± 69.9 (162.1–234.1)	203.0 ± 77.3 (167.7–248.7)	271.3 ± 104.9 (233.1–338.3)	321.1 ± 81.5 (280.6–361.7)
Nondominant	192.5 ± 69.5 (167.3–238.2)	214.2 ± 70.3 (188.7–259.5)	278.3 ± 87.2 (247.1–330.3)	318.2 ± 81.9 (277.4–358.9)

* Significant differences between groups (two-way analysis of variance test).
Values ± SD are expressed as mean (95% confidence interval).

a previous study [35] that evaluated peripheral nerve tissue in 20 breast cancer survivors before and 6 weeks after surgery, with a significantly reduced ROM found during $ULNT_{MEDIAN}$ in the operated side. However, our results do not agree with Sterling et al. [9], who found bilateral mechanosensitivity in subjects with whiplash-associated disorder. This fact may be explained by the existence of brachial plexopathy caused by the administration of radiation therapy [16,17] as the medical treatment. This plexopathy can occur more significantly in the affected side, where the radiotherapy is applied than in the nonaffected side. The physical trauma associated with the surgical procedure can elicit an influx of inflammatory mediators into the area associated with the surgery. Additionally, postsurgical edema may lead to irritation of the nervous tissue [41].

The movements performed during ULNTs elicit strain and compression on the nerves and are thus considered plausible tests for detecting peripheral neuropathic pain [42]. Decreased ROM during ULNTs appears to be due to increased muscle activity as a protective mechanism of mechanosensitivity in nerve tissue [43,44]. This process occurs as a consequence of changes in the dorsal horn interneurons involved in reflex pathways to motor neurons [45]. Recently, Smoot et al. [28] studied mechanosensitivity in women after breast cancer treatment and found significant reductions in elbow extension ROM during $ULNT_{MEDIAN}$ in patients with pain and lymphedema, though the results were not statistically significant in patients with pain but without lymphedema. Our results partially agree with this work, as the patient group did not present lymphedema at the moment of the research but did have neck–shoulder pain.

Several limitations should be recognized in this study. No prospective data were obtained from the patients prior to surgery. In addition, the study design does not provide information about the possible cause–effect relationship between widespread pressure pain hyperalgesia and reductions in ROM during ULNTs detected in the patient group. One of the main objectives of the study was not to classify groups of patients in positive or negative ULNTs but to attempt to describe reductions in ROM during tests. The structural differentiation at the end of the tests and the use of imaging techniques should be considered for future studies, as they would strengthen the results of the current work [43]. Finally, for future studies, it would be important to add a large follow-up period to provide more information about possible changes in peripheral and central sensitization in the breast cancer population after

Table 3 Range of motion (degrees) in patients with postmastectomy pain and healthy controls

	$ULNT_{median}$	$ULNT_{radial}$	$ULNT_{ulnar}$
Patients with postmastectomy pain			
Affected	131.6 ± 15.4 (124.7–138.4)*	87.0 ± 15.3 (80.2–93.8)*	86.4 ± 17.6 (78.5–94.2)*
Nonaffected	156.9 ± 7.6 (153.5–160.2)	101.6 ± 14.8 (95.0–108.2)	111.8 ± 13.5 (105.7–117.8)
Healthy control participants			
Dominant	154.5 ± 15.5 (147.6–161.5)	100.4 ± 23.5 (89.9–110.9)	109.4 ± 18.6 (101.1–117.7)
Nondominant	158.9 ± 12.8 (153.2–164.6)	104.3 ± 28.3 (91.7–116.8)	110.0 ± 23.7 (99.4–120.5)

* Significant differences between groups and between sides (two-way analysis of variance test).
Values ± SD are expressed as mean (95% confidence interval).

treatment. Nevertheless, this study highlights knowledge about sensitization processes.

Clinical Implications

The findings of the current study show the need of rehabilitation programs for the specific treatment of neural tissue in breast cancer patients and not only targeted to muscular tissue. Traditionally, clinicians do not adequately assess the nervous component of pain in breast cancer patients, and treatments are focused on muscular tissue. In view of our results, health care providers should assess upper limb ROM, quality of motion, and neural hypersensitivity in breast cancer survivors to identify possible peripheral nerve implication and neurodynamics, to thereby be able to design rehabilitation programs that take into account the neural component of pain in this population. In addition, several medical treatments are proposed to minimize peripheral neuropathy in cancer patients [39] which, together with physical treatment, could be a preferred option for this population.

Conclusion

The results of the present study show that breast cancer survivors present bilateral and widespread neural hypersensitivity, as they did in muscular tissue in previous studies. Breast cancer survivors demonstrate a reduction in ROM during ULNTs in the affected side.

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Pressure Pain Sensitivity Maps of the Neck-Shoulder Region in Breast Cancer Survivors

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Pressure Pain Sensitivity Maps of the Neck-Shoulder Region in Breast Cancer Survivors

ABSTRACT

Background: Pain is one of the most reported symptoms following breast cancer surgery. Recent studies have reported an increased sensitivity to pain in the upper limb as a sign of a central sensitization mechanism in women after standard treatment of breast cancer. This study was hypothesized that breast cancer survivors compared with matched healthy controls would exhibit bilateral hypersensitivity to pressure pain in both frontal and dorsal part of the neck-shoulder region.

Methods: Twenty-two breast cancer survivors (BCS) and 22 matched controls participated. A numeric pain rating scale of the neck-shoulder area and pressure pain thresholds (PPTs) were assessed bilaterally over 28 points in frontal and dorsal neck-shoulder area. Topographical pain sensitivity maps of the upper trapezius, pectoral and anterior deltoid areas were computed.

Results: A 3-way analysis of variance was carried out to evaluate differences in PPTs. BCS reported spontaneous neck pain (mean ± SD 3.6 ± 2.8), pain in the affected shoulder (4.3 ± 2.7) and in the non-affected shoulder (0.9 ± 1.8). Additionally, BCS exhibited bilaterally lower PPTs in all the measurement points as compared with controls ($P < 0.05$). PPTs were lower at superior part of the trapezius muscle ($P < 0.001$), musculotendinous insertion, anterior part of the deltoid muscle ($P < .001$), and tendon of the pectoral muscle ($P < .001$) as compared with controls.

Conclusions: The results confirm the sensitization processes in BCS and give preliminary evidence to most sensitive areas in the superior part of upper trapezius and musculotendinous insertion of pectoral muscle.

INTRODUCTION

Upper body pain is an important functional post-treatment disorder in breast cancer survivors (Belfer et al., 2013; Forsythe et al., 2013; Goodwin et al., 2014; Schou Bredal et al., 2014). The pain may appear immediately after surgery of breast cancer or a few years later (Hayes et al., 2012; Stubblefield et al., 2014). Pain disorders reduce physical functioning and result in adverse psychosocial and social effects with a significant negative consequence on quality of life (Rietman et al., 2004; Ewertz et al., 2011). The reported incidence of pain ranges from 25-60% in breast cancer survivors (Andersen et al., 2011; Schreiber et al., 2013), and 12–29% of those report pain attributed to cancer after more than 6 years (Schimtz et al., 2012).

A large number of studies have demonstrated adverse upper body symptoms associated with breast cancer treatments. Upper extremity pain disorders such as postsurgical pain, rotator cuff disease, lateral epicondylitis, adhesive capsulitis, arthralgias, cervical radiculopathy, brachial plexopathy, neuropathy, postmastectomy pain syndrome, lymphedema, axillary web syndrome and deep vein thrombosis have been reported to affect breast cancer survivors (Stubblefield et al., 2006). Langford et al. described two types of pain after the breast cancer surgery with different characteristics, arm pain and breast pain, and postulated that both types produce important changes in sensation (Langford et al. 2014). The standard treatment with breast surgery, radiotherapy and neurotoxic chemotherapy has a complex relationship with common neuromuscular, musculoskeletal and lymphovascular disorders. The specific etiologies of pain induced by breast cancer treatment are complex. Axillary dissection can cause peripheral nerve dysfunction and scar tissue formation (Cheville et al., 2007), radiation therapy can induce fibrosis of connective tissue around peripheral nerves and cause damage to capillary blood vessels resulting in ischemia and changes in myelinated and unmyelinated axons (Johansson et al., 2000; Bajrovic et al., 2004). Further, exposure to neurotoxic chemotherapy may increase the risk of peripheral sensory disturbances (Andersen et al.,

2012). Recent studies have reported pressure pain hypersensitivity, i.e., increased sensitivity to pain in the upper limb as a sign of a central sensitization mechanism in women after standard treatment of breast cancer, i.e., a combination of axillary dissection, radiotherapy, and chemotherapy (Fernández-Lao et al., 2010; Caro-Morán et al., 2014).

Pressure algometry is a technique with high reliability enabling the assessment of the sensitivity of deep somatic structures to mechanical pain (Fischer et al., 1998; Ylinen et al., 2007). The recording of multiple of pressure pain thresholds (PPTs) based on a geometric template can be used to generate pressure pain maps and depict hypo- or hypersensitive body areas (Binderup et al., 2009). Numerous studies have shown a relation between the areas most sensitive to pressure pain and the development of hyperalgesia. (e.g., Nie et al., 2005; Fernández de las Peñas et al., 2009). The shoulder region and more specifically the pressure pain maps of the upper trapezius and infraspinatus have been studied in healthy participants with experimentally induced musculoskeletal pain and patients with musculoskeletal neck-shoulder pain (Ge et al., 2008; Binderup et al., 2010a; Binderup et al., 2011; Kawczynski et al., 2012,). Interestingly, bilateral hypersensitivity to pressure pain supporting the involvement of central sensitization mechanisms in patients with unilateral pain has been reported (Ge et al., 2008). However, bilateral changes in pressure pain sensitivity in the shoulder region including the dorsal (upper trapezius) and the frontal (pectoralis major and deltoid muscles) part of the neck-shoulder region have not yet been studied in breast cancer survivors.

Thus, the aim of the present study was to report PPT topographical maps of the frontal and dorsal parts of the shoulder region and locate pressure pain sensitive areas in breast cancer survivors compared with matched healthy controls. In this cross-sectional study, it was hypothesized that compared with matched healthy controls breast cancer survivors would exhibit bilateral hypersensitivity to pressure pain in both the frontal and dorsal part of the neck-shoulder region.

METHODS

Participants

Forty-four women participated in the current study. Twenty-two breast cancer survivors were recruited from the Department of Oncology at the Hospital Virgen de las Nieves in Granada, Spain. The inclusion criteria for breast cancer survivors were: 1) primary diagnosis of breast cancer (grades I-IIIA), 2) adult women at least 18 years of age, 3) having received breast surgery such as lumpectomy, quadrantectomy or unilateral mastectomy at least 6 months before the start of the study, 4) women without signs of recurrence of breast cancer, 5) adjuvant therapy (radiation, cytotoxic chemotherapy) completed at least 3 months before the inclusion, except hormone therapy, and 6) presence of pain in neck and/or shoulder/axillary which began after the breast cancer treatments. Exclusion criteria were: 1) breast surgery for cosmetic reasons or prophylactic mastectomy, 2) bilateral breast cancer, 3) recurrence of cancer, 4) lymphedema, 5) other adverse medical conditions (i.e., arthritis), or 6) previous diagnosis of fibromyalgia syndrome.

Participants included in the control group were healthy female volunteers responding to an announcement at the University of Granada. The controls were matched by age with the subjects from the breast cancer survivor group. The exclusion criteria for the controls were the presence of signs or symptoms of musculoskeletal pain, history of pain or trauma in the neck, shoulder, arm, upper extremity or diagnosis of any systematic disease.

The study protocol was approved by the Granada Research Ethics Committee of Granada and followed the Helsinki Declaration. Participants were informed about the procedures and signed the form of informed consent prior to participation. The participants were scheduled to complete medical records, undergo a physical examination and fulfill a medical questionnaire including information on anthropometrics, surgical and dominant side, comorbidity, socio-educational level, marital status, and previous oncology treatments.

The sample size was calculated using Epidat3.0, (Xunta de Galicia, Spain). To detect a significant clinical difference of 20 % on PPT over different points between groups and assuming an alpha level of 0.05 and a power of 80 % (estimated inter-individual coefficient of variation for measure of 20 %), 18 participants were required in each group. Assuming a drop-out of 20-30 %, it was decided to enrol 20-24 participants per group.

Pain Intensity

The intensity of pain in the neck and left and right shoulder was scored by each participant using a 10 cm Numeric Pain Rating Scale (NPRS) where 0 corresponded to no pain and 10 the maximum tolerable pain (Jensen et al., 1999). The cut-off scores used as reference in NPRS were: 0 no pain; 1-3 mild; 4-6 moderate; 7-10 severe pain (McCaffery et al., 1989). The participants were instructed not to take pain-relieving medication or muscle relaxants 24 hours before the PPT assessments.

Pressure Pain Threshold

The participants were comfortably seated with their arm on the armrest and the elbows flexed at 90°. A pressure algometer (Somedic AB, Farsta, Sweden) with a 1 cm^2 tip diameter and a constant pressure rate of 30kPa/s was used to measure the PPT levels. The participants were instructed to press a handheld button to indicate when the sensation changed from pressure to pain. The algometer was calibrated prior to each series of assessments. All assessments were performed by the same researcher. The pressure points were marked with a wax pencil. A total of 28 points on the frontal and dorsal part of the neck-shoulder region (fifteen points over the upper trapezius muscle, six points over the anterior portion of the deltoid muscle, six points over the pectoralis major muscle and one point over the tibialis anterior muscle as a distant reference point (Fernández-Lao et al., 2011) were measured bilaterally on each participant with a 30 second resting period between assessments. The assessments were performed twice over two rounds in random order and a third time if the point assessed had a coefficient of variance over 0.2 (Binderup et al., 2009). The mean PPT values were calculated.

Mapping of the Dorsal Region of the Shoulder

In agreement with Binderup et al. (Binderup et al., 2010a) and Kawczynski et al. (Kawczynski et al., 2012), the distance *d* between C7 and acromion was measured for each participant to compute the interdistance between the 15 points covering the upper trapezius. Points 1, 3, 5, 10, and 15 corresponded to musculotendinous sites, and points 2, 4, 6, 7, 8, 9, 11, 12, 13, and 14 corresponded to muscle belly sites. Adjacent PPT points were separated by one-sixth of the distance *d* except between points 1-2 and points 3-4 where the horizontal distance was one-seventh of distance *d*. Further, the horizontal distance between the spine or the acromion processes and the adjacent points on the muscle was one-twelfth of *d* (**Figure 1**).

Mapping of the Frontal Region of the Shoulder

The acromion was used as the reference point to start designing the grid on the deltoid muscle. Point 1 was marked below the acromion at one-twelfth of the distance *d*. Thereafter, 3 points downwards vertically separated by one-sixth of the distance *d* were marked and labelled point 2, 3 and 4. Points 5 and 6 were symmetrically allocated at one-sixth of the distance *d* medial to point No. 3 and 4 respectively (**Figure 2**). The coracoid bone was the reference point for drawing the grid on the pectoralis major muscle. Point 9 was marked below the coracoid at one-twelfth of the distance *d*. Thereafter, 3 points downwards vertically separated by one-sixth of the distance *d* were marked and labelled point 10, 11 and 12. Points 7 and 8 were symmetrically located at one-sixth of the distance *d* external to point No. 10 and 11 respectively. The pressure pain maps were generated based on the mean PPTs using Matlab (The Mathworks, Natick, MA, USA). The x and y coordinates of each point were measured for one representative participant (Figures 1 and 2). The z coordinates corresponded to the

average 27 PPT points (15 and 12 points for the dorsal and frontal part respectively) of the 22 participants. An inverse distance weighted interpolation was applied to obtain the PPT distribution over the shoulder region (Binderup et al., 2009). This method enables the detection of spatial differences in the pressure sensitivity of deep structures (Binderup et al., 2011).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 20.0. The results are expressed as mean, standard deviations (SD) and confidence interval (95% CI). The Kolmogorov-Smirnov test revealed that PPTs showed a normal distribution (P > .05) supporting the use of parametric A multilevel 3-way ANOVA test to detect differences in PPTs assessed with point (1 to 28) and side (affected/non-affected in breast cancer survivors, dominant/non-dominant in controls) as the within-subject factors and group (breast cancer survivors or controls) as the between-subject factor. Post hoc comparisons were conducted with the Bonferroni test. The statistical analysis was conducted at a 95% confidence level and a P value less than .05 was considered statistically significant.

RESULTS

Twenty-two women aged 31-63 years (mean ± SD 48.8 ± 7.7) who had undergone breast surgery after a breast cancer diagnosis and twenty-two healthy matched controls, aged 30-64 years (49.1 ± 8.2) participated in the study. Eleven (50%) breast cancer survivors had suffered from cancer on the right side (affected side), whereas the remaining 11 (50%) had suffered from cancer on the left side. At the time of the data collection, seven breast cancer survivors (31.8%) were taking ibuprofen, four (18.2%) were taking paracetamol and three (13.6%) were taking metamizol. The remaining breast cancer survivors (40.9%) were not taking any medication. Thirteen (59.1%) breast cancer survivors reported moderate or severe neck pain, fifteen (68.2%) showed moderate or severe affected shoulder pain and three (13.6%) had no shoulder pain. The group of breast cancer survivors exhibited spontaneous neck pain of (3.6 ± 2.8), affected shoulder pain of (4.32 ± 2.7) and non-affected shoulder pain of (0.9 ± 1.8).

A summary of the principal descriptive results and differences between the groups is shown in **Table 1**.

The ANOVA detected significant differences between groups (F = 181,303; *P* < .001), points (F = 21.660; *P*< .001), and sides (F = 7.791; *P* =.005) for PPT levels. In addition, a significant interaction between group × side was found (F = 13.587; *P* < .001), but not between group × point (F = 0.766; *P* = .794) and point × side (F = .464; *P* = .991). Further, no interaction between group × point × side (F = .182; *P* = 1.000) was found. The post hoc comparisons revealed: 1) lower PPT levels over the affected side in points 5,6,7,8,9,10,11,14, and 15 of trapezius; points 1,2, and 3 of deltoid anterior; points 7,10,11, and 12 of pectoralis major; and in tibialis anterior muscle (P<.05) in breast cancer survivors but not in healthy controls (**Table 2, 3** and **4**); 2) breast cancer survivors exhibited lower PPT levels in the measurement points 7,10, and 12 (*P* < .05) within trapezius. Breast cancer survivors also had lower PPT levels over points 2,3,5, and 6 (*P* < .05) within the deltoid anterior and points 7, 8, 10, 11, and 12 within the pectoralis major muscle (**Table 2, 3** and **4**) when compared with healthy controls; 3) lower PPT over point 2 (superior fibres of the trapezius muscle) when compared with the remaining points (*P* < .001) (**Figure 3**); higher PPT over point 1 (musculotendinous insertion of the deltoid muscle; *P* < .001) when compared with the remaining points; lower PPT over point 6 (anterior fibres of the deltoid anterior muscle; *P* < .001) when compared with all the remaining points; and lower PPT over point 12 (tendon of the pectoral muscle; *P* < .001) when compared with all the remaining points (**Figure 4**).

DISCUSSION

The present study was the first to apply topographical pressure sensitivity maps from the shoulder region in breast cancer survivors. The findings revealed a generalized bilateral hyperalgesia on both the frontal and dorsal region of the shoulder compared with healthy matched controls. These results are in line with the hypothesis suggesting that breast cancer survivors would exhibit bilateral hypersensitivity to pressure pain in the shoulder region including the dorsal and the frontal part compared with matched healthy women.

The use of multiple PPT assessments enables generation of pressure pain maps and pressure pain topographical maps with the purpose of detecting particular areas of pain sensitivity (Binderup et al., 2010b). This relatively new modality of pain imaging revealed that the breast cancer survivor group was characterized by an upper-lower symmetrical pressure pain threshold gradient in the trapezius muscle. The points most sensitive to pressure were situated over the muscle belly site and the muscle tendon junction on both the non-affected and affected sides, whereas in healthy controls the pain sensitivity maps had similar spatial distribution on both non-dominant and dominant side. Further, breast cancer survivors with postmastectomy pain were also characterized by a lower-medial to upper-external pressure pain gradient with the most sensitive point to pressure situated over the muscle tendon junction of the pectoralis major on the affected side compared with the non-affected side. For the matched control group the pressure pain maps had similar spatial distributions with no significant difference between non-dominant and dominant side.

Thirteen (59.1%) breast cancer survivors reported moderate or severe neck pain, 15 (68.2%) showed moderately or severely affected shoulder pain. Finally, three (13.6%) breast cancer survivors also reported pain from the non-affected shoulder. These pain ratings are in line with the bilateral pressure hypersensitivity found in the trapezius area (point 2, upper trapezius) both at the occipital insertion and muscle belly. This finding suggests central sensitization in women who have survived breast cancer in agreement with results previously reported for women who had undergone either type of breast cancer surgery (Gottrup et al., 2000; Fernández-Lao et al., 2011). Hyperexcitability of the central nervous system after breast cancer surgery is clinically sustained in previous studies which have already shown that many patients suffer from widespread diffuse persistent pain after surgery (Carpenter et al., 1998; Caro-Moran et al., 2014). According to the current results, the occipital insertion of the upper trapezius (points 1-2) appeared to be the most sensitive place in breast cancer survivors. This is in line with data obtained from healthy females (Binderup et al., 2010a) even though lower PPTs in female cancer survivors should be noted. Another relevant finding was seen in the pressure pain maps of the frontal area. The lowest PPTs were concentrated around the tendon of the pectoralis major muscle (points 11-12) in the affected side within the breast cancer survivor group. This decrease in PPTs may be a result of the surgical procedure (Wadd et al., 1998; Johansson et al., 2002). Gottrup et al. (Gottrup et al., 2000) have reported that the damage caused in small nerve fibres during the surgery procedure induces peripheral sensitization and contributes to clinical pain and sensory disturbances in postmastectomy pain patients. Another explanation may be found in the fact that widespread changes in pain sensitivity can be caused by the chemotherapy given during the treatment for breast cancer. Chemotherapy can lead to peripheral neuropathy and changes in afferent vagal activity (Partridge et al., 2004). This explanation substantiating the role of central sensitization is also supported by the lower PPT in the tibialis anterior muscle measured in postmastectomy pain patients compared with matched controls.

All in all, these findings indicate that breast cancer survivors have a specific topographical pressure sensitivity map characterized by bilateral pressure pain hypersensitivity in the upper trapezius area and pressure hypersensitivity over the tendon of the pectoralis major muscle on the affected side.

This study has some limitations; firstly a greater sample size is required to permit a more general interpretation of the results. Secondly, PPT assessments were not collected prior to surgery. Prospective studies assessing the changes in mechanical pain sensitivity are thus warranted in breast cancer survivors. Further, the spatial distribution of pressure pain sensitivity in breast cancer survivors without lymphedema has been described, and an assessment of PPTs in other breast cancer survivors will expand the current knowledge. For future studies it would be important to add a follow-up period and an intervention consisting of, e.g., physical training to provide more information about possible changes in the pressure pain sensitive maps among breast cancer survivors.

CONCLUSION

The results from the current work add evidence to support the presence of the central sensitization processes of the nociceptive system in breast cancer survivors. A generalized bilateral hyperalgesia in both the frontal and dorsal region of the neck and shoulder (superior part of the upper trapezius and musculotendinous insertion of pectoral muscle) was found in breast cancer survivors compared with healthy matched controls.

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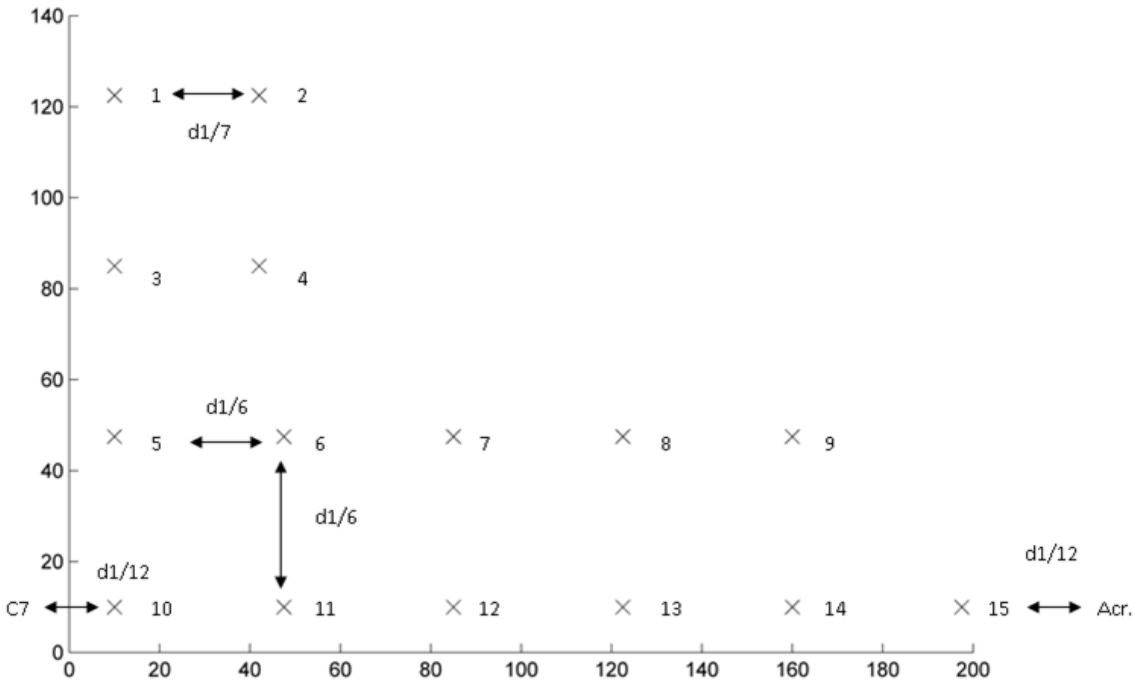

Figure 1. Schematic representation of the grid for the pressure pain threshold (PPT) registers. PPTs were measured over 15 points (1-15) located on the trapezius muscle. d= Distance between C7 and acromion.

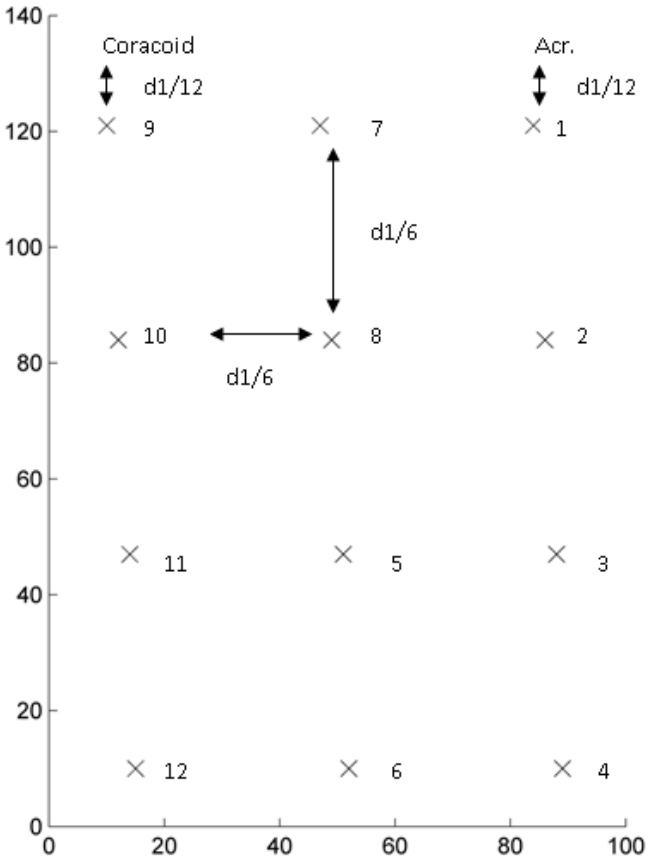

Figure 2. Illustration of the points used to assess pressure pain thresholds (PPTs) that formed a 3 X 4 matrix. Six points (1-6) located over deltoid muscle and other six points (7-12) located over the pectoralis major muscle. d= Distance between C7 and acromion.

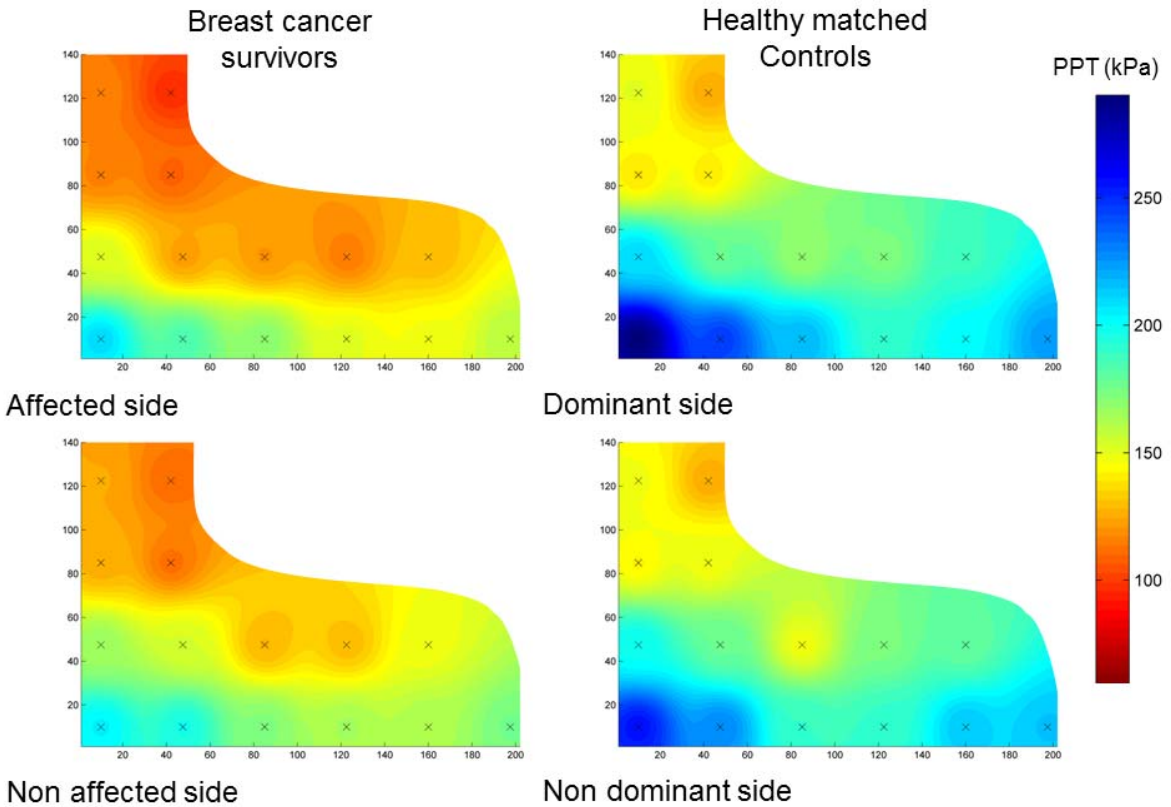

Figure 3. Pressure Pain Treshold (PPT) maps from the dorsal part of the shoulder covering the upper trapezius muscle in breast cancer survivors and matched healthy controls. Units on axis are in kPa.

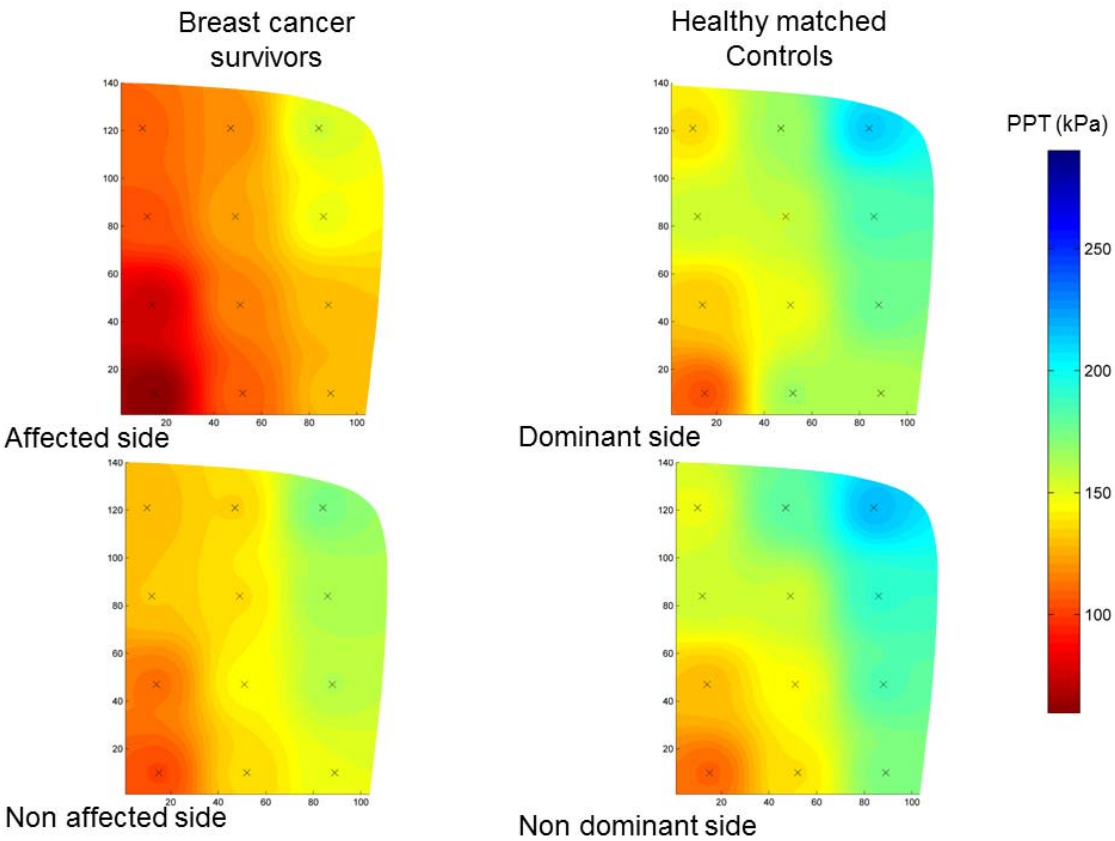

Figure 4. Pressure Pain Treshold (PPT) maps from the frontal part of the shoulder partly covering the deltoid anterior and the pectoralis major muscle in breast cancer survivors and matched healthy controls. Units on axis are in kPa.

Table 1. Participant demographic and clinical characteristics

Variable	Breast cancer survivors (N=22)	Healthy control participants (N=22)	*P* value
Age (years)	48.8 ± 7.7 (45.4-52.2)	49.09 ± 8.2 (45.4-52.7)	.910
Body mass (kg)	66.7 ± 10.76 (61.9-71.4)	71.5 ± 12.5 (65.9-77.0)	.178
Height (cm)	162.3 ± 6.1 (159.6-165.0)	162.6 ± 5.1 (160.3-164.9)	.853
Marital status, N (%)			.565
Married	18 (81.8%)	18 (81.8%)	
Single	4 (18.2%)	3 (13.6%)	
Divorced	0	1 (4.5%)	
Educational level, N (%)			.009*
Primary studies	5 (22.7%)	0	
Secondary studies	8 (36.4%)	4 (18.2%)	
University studies	9 (40.9%)	18 (81.8%)	
Occupational status, N (%)			.000*
Homemaker	4 (18.2%)	0	
Employed	4 (18.2%)	21 (95.5%)	
Sick leave	7 (31.8%)	0	
Not working due to the disease	7 (31.8%)	0	
Retired	0	1 (4.5%)	
Smoking status, N (%)			.519
Non-smoker	11 (50.0%)	12 (54.5%)	
Smoker	9 (40.9%)	6 (27.3%)	
Ex-smoker	2 (9.1%)	4 (18.2%)	
Alcohol status, N (%)			.018*
No consumption	10 (45.5%)	11 (50.0%)	
Consume monthly	4 (18.2%)	10 (45.5%)	
Consume weekly	8 (36.4%)	1 (4.5%)	
Menopausal status, N (%)			.000*
Pre-menopausal	1 (4.5%)	10 (45.5%)	
Post-menopausal	21 (95.5%)	12 (54.5%)	
Time since diagnosis (months)	26.0 ± 12.6 (20.4-31.7)		
Time since surgery (months)	20.6 ± 13.1 (14.7-26.4)		
Medical treatment, N (%)			
Radiotherapy	2 (9.1%)		
Chemotherapy	0		
Radiotherapy + chemotherapy	20 (90.9%)		
Type of surgery, N (%)			
Lumpectomy	8 (36.4%)		
Quadrantectomy	6 (27.3%)		
Unilateral mastectomy	8 (36.4%)		
Neck pain	3.5 ± 2.8 (2.29-4.80)	0.2 ± 0.5 (.03-.1)	.000*
Affected shoulder pain	4.3 ± 2.7 (3.1-5.5)	0.2 ± 0.5 (-.1-0.1)	.000*
Non-affected shoulder pain	.8 ± 1.7 (0.1-1.6)	0	.026*

*Significant differences between groups and between sides (χ^2 test).
Values ± SD are expressed as mean (95% confidence interval) and absolute porcentages.

Table 2. Pressure Pain Thresholds (PPT, kPa) over the upper trapezius muscle (points 1-15) in breast cancer survivors and healthy controls

	BREAST CANCER SURVIVORS		HEALTHY CONTROLS PARTICIPANTS	
	AFFECTED	**NONAFFECTED**	**DOMINANT**	**NONDOMINANT**
PPT point 1	116.1 ± 58.2	124.6 ± 60.1	150.2 ± 47.4	146.8 ± 47.3
	(90.2-141.9)	(97.9-151.2)	(129.2-171.2)	(125.8-167.8)
PPT point 2	97.2 ± 45.4	110.9 ± 51.6	125.5 ± 37.8	125.9 ± 35.6
	(77.0-117.3)	(88.0-133.8)	(108.7-142.3)	(110.0-141.7)
PPT point 3	116.3 ± 66.2	125.7 ± 61.5	138.7 ± 44.0	142.4 ± 40.8
	(86.9-145.7)	(98.4-153.0)	(119.1-158.2)	(124.2-160.5)
PPT point 4	109.4 ± 61.6	112.2 ± 54.6	140.9 ± 42.8	147.1 ± 57.6
	(82.1-136.8)	(87.9-136.4)	(121.9-159.9)	(121.6-172.7)
PPT point 5	152.7 ± 90.1*	166.9 ± 94.7*	210.3 ± 59.1	200.4 ± 69.6
	(112.8-192.7)	(124.9-208.9)	(184.1-236.6)	(169.5-231.3)
PPT point 6	122.3 ± 64.5*	153.4 ± 96.0*	178.4 ± 52.0	177.9 ± 54.6
	(93.7-150.9)	(110.8-196.0)	(155.3-201.4)	(153.7-202.2)
PPT point 7	120.6 ± 69.8*	127.8 ± 62.1*	168.0 ± 40.7	147.8 ± 42.5
	(89.6-151.6)	(100.3-155.4)	(149.9-186.0)	(128.9-166.6)
PPT point 8	115.1 ± 63.8*	129.5 ± 69.7*	173.1 ± 56.0	174.0 ± 61.5
	(86.7-143.4)	(98.5-160.4)	(148.2-197.9)	(146.7-201.3)
PPT point 9	129.2 ± 75.2*	148.1 ± 73.3*	188.7 ± 51.8	178.9 ± 62.0
	(95.8-162.6)	(115.6-180.6)	(165.7-211.7)	(151.4-206.4)
PPT point 10	210.0 ± 111.6*	204.6 ± 91.7*	290.3 ± 69.8	257.2 ± 86.9
	(160.5-259.6)	(164.0-245.3)	(259.3-321.3)	(218.7-295.8)
PPT point 11	184.9 ± 108.3*	197.2 ± 87.8*	245.7 ± 54.0	229.0 ± 53.5
	(136.8-232.9)	(158.3-236.2)	(221.7-269.7)	(205.3-252.8)
PPT point 12	170.6 ± 90.5*	172.5 ± 78.7*	217.4 ± 48.9	189.8 ± 53.4
	(130.4-210.7)	(137.6-207.4)	(195.7-239.1)	(166.1-213.5)
PPT point 13	150.9 ± 85.6	164.6 ± 89.0	191.4 ± 29.2	191.5 ± 59.5
	(112.9-188.9)	(125.1-204.1)	(178.4-204.4)	(165.1-217.8)
PPT point 14	147.5 ± 79.9*	163.4 ± 87.2*	203.3 ± 43.6	214.6 ± 69.2
	(112.1-183.0)	(124.7-202.1)	(183.9-222.6)	(183.9-245.3)
PPT point 15	160.4 ± 86.2*	175.7 ± 82.8*	224.8 ± 73.1	215.3 ± 66.8
	(122.1-198.6)	(138.9-212.4)	(192.4-257.2)	(185.7-245.0)

*Significant differences between groups and between sides (two-way analysis of variance test).
Values ± SD are expressed as mean (95% confidence interval).

Table 3. Pressure Pain Thresholds (PPT, kPa) over the deltoid muscle area (points 1-6) in breast cancer survivors and healthy controls

	BREAST CANCER SURVIVORS		HEALTHY CONTROLS PARTICIPANTS	
	AFFECTED	NONAFFECTED	DOMINANT	NONDOMINANT
PPT point 1	154.2 ± 86.9*	173.3 ± 86.0*	212.8 ± 43.0	217.4 ± 63.7
	(115.7-192.8)	(135.2-211.5)	(193.7-231.8)	(189.1-245.6)
PPT point 2	147.4 ± 87.3*	163.4 ± 88.3*	183.4 ± 54.6	190.3 ± 56.0
	(108.6-186.1)	(124.2-202.6)	(159.2-207.6)	(165.5-215.2)
PPT point 3	130.8 ± 72.0*	160.9 ± 92.6*	177.8 ± 53.2	183.8 ± 50.3
	(98.9-162.8)	(119.8-202.0)	(154.2-201.4)	(161.5-206.2)
PPT point 4	129.9 ± 74.4	149.8 ± 82.7	161.1 ± 40.6	173.5 ± 50.2
	(96.9-162.9)	(113.1-186.4)	(143.1-179.1)	(151.3-195.8)
PPT point 5	116.4 ± 67.0*	143.8 ± 80.8*	151.0 ± 45.0	145.5 ± 59.5
	(86.6-146.1)	(107.9-179.7)	(131.0-171.0)	(119.1-171.9)
PPT point 6	108.9 ± 61.4*	136.7 ± 89.1*	148.0 ± 52.1	138.8 ± 45.6
	(81.7-136.1)	(97.1-176.2)	(124.8-171.1)	(118.5-159.0)

*Significant differences between groups and between sides (two-way analysis of variance test).

Values ± SD are expressed as mean (95% confidence interval).

Table 4. Pressure Pain Thresholds (PPT, kPa) over the pectoralis major area (points 7-12) in breast cancer survivors and healthy controls

	BREAST CANCER SURVIVORS		HEALTHY CONTROLS PARTICIPANTS	
	AFFECTED	**NONAFFECTED**	**DOMINANT**	**NONDOMINANT**
PPT point 7	117.6 ± 63.2*	135.0 ± 75.2*	164.8 ± 46.7	180.4 ± 60.6
	(89.6-145.7)	(101.6-168.4)	(144.1-185.6)	(153.5-207.3)
PPT point 8	123.8 ± 74.5*	138.7 ± 80.4*	156.8 ± 38.5	155.4 ± 62.4
	(90.8-156.9)	(103.0-174.3)	(139.7-173.9)	(127.7-183.1)
PPT point 9	108.2 ± 67.2	128.3 ± 57.6	137.3 ± 45.2	148.3 ± 54.0
	(78.4-138.0)	(102.7-153.8)	(117.3-157.4)	(124.3-172.2)
PPT point 10	105.7 ± 67.3*	131.7 ± 64.5*	156.0 ± 56.7	156.0 ± 54.0
	(75.8-135.5)	(103.0-160.3)	(130.8-181.1)	(132.0-179.9)
PPT point 11	74.7 ± 58.4*	112.5 ± 58.9*	132.4 ± 60.6	130.1 ± 55.1
	(48.8-100.6)	(86.3-138.6)	(105.6-159.3)	(105.6-154.6)
PPT point 12	59.4 ± 41.2*	102.2 ± 57.9*	104.9 ± 32.2	109.2 ± 45.0
	(41.1-77.7)	(76.5-128.0)	(90.5-119.2)	(89.3-129.2)

*Significant differences between groups and between sides (two-way analysis of variance test).

Values ± SD are expressed as mean (95% confidence interval).

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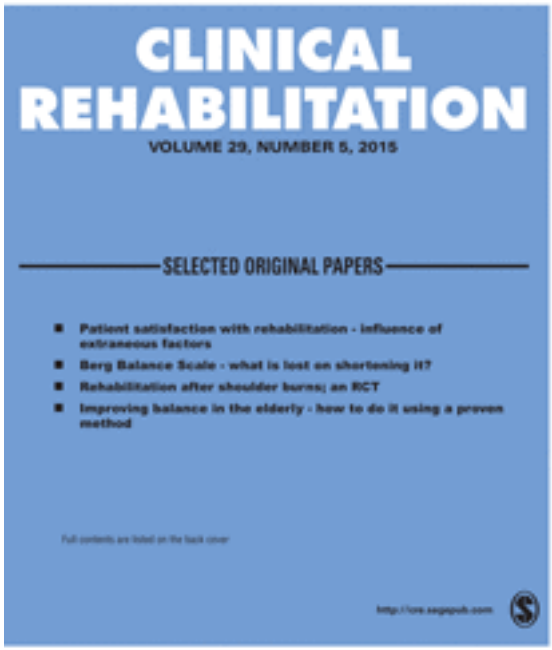

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Aquatic exercise in a chest-high pool for hormone therapy-induced arthralgia in breast cancer survivors: a pragmatic controlled trial

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Abstract

Objective: To investigate the impact of aquatic exercise on pressure pain threshold in breast cancer survivors with hormone therapy-associated arthralgia.
Design: Single-blind, controlled trial.
Setting: Two major metropolitan hospitals and a Sport and Spa Club in Granada, Spain.
Subjects: Forty women aged 29–71 years with stage I–III breast cancer who reported arthralgia.
Intervention: Patients were allocated alternately to either aquatic exercise in a chest-high pool or usual care while on the waiting list; control patients received treatment later. The two-month hydrotherapy intervention consisted of 24 sessions 3 days per week. Each session included 5 minutes of warm-up, 15–20 minutes of aerobic exercise, 15 minutes of mobility exercise and 20 minutes of recovery techniques.
Main measures: Pressure pain threshold at neck, shoulder, hand and leg were evaluated as primary outcomes. Cancer-related fatigue, as measured by the Piper Fatigue Scale, body mass index and waist circumference were secondary outcomes. A 2 × 2 repeated-measure ANCOVA was used in this study.
Results: No adverse events or development of worsening of pain was observed. Almost all the participants in the intervention group (89%) adhered to the hydrotherapy programme. Participants experienced a decrease in pressure pain threshold measured in neck, hand, shoulder and leg, as measured by algometry pressure, and waist circumference; all $P < 0.05$. Cancer-related fatigue ($P = 0.06$) and body mass index ($P = 0.42$) did not show significant improvement.
Conclusions: These data suggest that hydrotherapy in a chest-high pool may reduce the pain threshold and waist circumference in breast cancer survivors with hormone therapy-associated arthralgia.

Keywords

Cancer, exercise, fatigue, hydrotherapy

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Introduction

Hormone therapy for carcinoma of the breast may be associated with debilitating arthralgia in a small proportion of users. The actual incidence of arthralgias or musculoskeletal symptoms in breast cancer survivors using hormone therapy is not known, though such symptoms have been reported to be between 5% and 50%.[1,2] These arthralgias appear more commonly with aromatase inhibitor than with tamoxifen.[3–5] Nevertheless, a recent study has stated that arthralgia is a debilitating symptom consistently reported by a small, yet significant, proportion of tamoxifen users,[6] with a profile similar to that of examestane (third generation of aromatase inhibitors) with respect to arthralgia incidence.[7]

Arthralgia is one of the most prevalent causes reducing adherence to hormone therapy in breast cancer patients.[8,9] Clinicians have tried a variety of interventions, though it is not clear that any of these interventions has had a dramatic effect on these symptoms.[4] A possible treatment option for arthralgia may be gentle exercise. Yoga intervention has shown effectiveness in reducing pain and improving balance and flexibility in breast cancer survivors with arthralgia.[10] This study was limited due to a lack of an adequate control group.

Aquatic exercise is a popular non-pharmacologic modality used for treating a variety of conditions, including musculoskeletal pain.[11] The pain-relieving properties of hydrotherapy may be mediated by buoyancy that significantly decreases weight bearing and stress on weight-bearing joints, bones, and muscles.[12] Clinical trials have found that patients with different conditions such as fibromyalgia,[13] pain associated with multiple sclerosis,[14] rheumatoid arthritis[15] or osteoarthritis[16] have less pain when hydrotherapy is used as a pain-relieving treatment. Different resources have been used, such as a deep-water pool in low back pain patients,[17] but other possibilities such as a chest-high pool have not been explored previously. As research in this area is limited, we conducted a preliminary study evaluating the use of hydrotherapy to relieve hormone therapy-associated arthralgia in breast cancer survivors.

Obesity[5] and cancer-related fatigue[18] have been associated with an increased incidence of muscle pain and arthralgias in breast cancer survivors. To the best of our knowledge, there are no previous studies analysing the effectiveness of hydrotherapy in improving body composition and cancer-related fatigue, as secondary outcomes, in breast cancer survivors using hormone therapy.

The specific aim of this study was to investigate the impact of aquatic exercise on pressure pain threshold, cancer-related fatigue and waist circumference in breast cancer survivors suffering hormone therapy-associated arthralgia.

Methods

The present study was a pragmatic, parallel group, controlled trial with allocation of participants into intervention ($n = 20$) or waiting list ($n = 20$, control group), according to order of arrival. Due to ethical reasons, it was not possible to randomize the patients. We had an ethical obligation with the Y010 Sport Centre to provide treatment to all patients willing to participate in the study, but due to limitations of resources we created a waiting list. For those subjects in the waiting list, data collected only during the control period were included in the current analysis. Throughout the study, all participants (including those in the control group) were encouraged to maintain their normal dietary habits. Control patients received treatment later. All patients gave informed consent for the study. This investigation was reviewed and approved by the University Hospital Virgen de las Nieves, Granada, Spain.

We recruited eligible patients from University Hospital Virgen de las Nieves and Hospital Clínico San Cecilio, Granada (Spain). Patients were recruited by two oncologists from the breast cancer unit. Because special facilities were required in this study (chest-high pool and complementary equipment) we contacted the Y010 Sport Club to carry out the study. Potential participants included Spanish-speaking women aged 18 years or older with stage I, II or IIIa breast cancer; and who were currently receiving aromatase inhibitors (anastrozole, letrozole or exemestane) or tamoxifen. Participants had to have had

joint pain attributable to hormone therapy following previous description of this syndrome.[4] Briefly, patients reported bilateral onset with symmetrical pain/soreness in their hands, knees, hips, lower back, shoulders and/or feet, with a score of at least 3 or more on an 11-point numerical rating scale[19] in the preceding two weeks together with early-morning stiffness and difficulty sleeping. Exclusion criteria included metastatic breast cancer (stage IV), having completed chemotherapy or radiation therapy less than four weeks prior to enrolment, joint pain attributed to inflammatory arthritis (such as rheumatoid arthritis, osteoarthritis or gout), having severe pain or non-inflammatory arthralgia prior to hormone therapy.

The two-month hydrotherapy intervention consisted of 24 sessions 3 days per week. The hydrotherapy intervention was carried out in an indoor pool sized 20 × 6 m, with 140 cm water depth, 30 ± 2°C of water temperature, and 33°C of room temperature. During this session, the participants also familiarized themselves with the use of the Borg Scale, which is a simple and reliable[20] method of rating perceived exertion used to control level of intensity during an exercise programme. Each aquatic therapy session lasted 60 minutes. A trainer exercise specialist and three physiotherapists supervised the participants. They were familiar with oncology exercise interventions. Each session included 5 minutes of warm-up, 15–20 minutes of aerobic exercise, 15 minutes of mobility exercise and 20 minutes of recovery techniques.

The aerobic exercises incorporated large muscle mass and consisted of different displacements, such as forward and backward jogging with arms pushing, pulling and pressing, leaps, leg crossovers and hopping movements focusing on travelling in multiple directions.

The mobility resistance exercises progressed throughout the programme by changing the number of repetitions per set (volume) and maximum range of motion without pain. Exercises were carried out at a reduced velocity and with appropriate axis orientation. Exercise included all possible joints implied in arthralgia induced by hormone therapy.

Participants were previously trained to relax by performing diaphragmatic breathing and concentrating on their breath. Massage techniques including superficial longitudinal strokes and local pressure over pain area were applied. Finally, full-body stretching exercises were performed at the end of each session. Participants followed usual care recommended by the oncologist in relation to a healthy lifestyle.

Sample size determination was performed with a software program (Tamaño de la Muestra 1.1, Madrid, Spain). The calculation was based on detecting between groups significant clinical differences of 20% on pressure pain threshold levels[21] with a level of 0.05, and a desired power of 80%, and an estimated interindividual coefficient of variation for pressure pain threshold measures of 20%. This generated a sample size of at least 16 participants per group. To accommodate possible dropouts before study completion, a total of 20 participants were included.

At the baseline and at the end of the eighth week, all patients were assessed for outcome variables. Pressure pain thresholds were used as the primary outcome variable as they have a reliable and adequate relationship with perceived joint pain.[21,22] Pressure pain threshold, defined as the minimal amount of pressure where a sensation of pressure first changes to pain,[23] was assessed with an electronic algometer (Somedic AB, Farsta, Sweden). The pressure was applied at a rate of approximately 30 kPa/s with a 1-cm^2 probe. Participants were instructed to press the switch when the sensation first changed from pressure to pain. The mean of three trials was calculated and used for the analysis. A 30-second resting period was allowed between each trial. The reliability of pressure algometry has been found to be high (intraclass correlation coefficient: 0.91, 95% confidence interval (CI) 0.82–0.97).[24] Pressure pain threshold levels were assessed over C5–C6 zygapophyseal joints, deltoid muscles (shoulder area), second metacarpals (hand area) and tibialis anterior (leg area) muscles by an assessor blinded to the allocation of the participants.

Cancer-related fatigue and body composition were assessed as secondary outcomes.

To assess cancer-related fatigue we used the Piper Fatigue Scale following recent guidelines.[25] The Piper Fatigue Scale is a validated tool assessing

cancer-related fatigue, and it was selected for its particular focus on related fatigue and pain.[26] The Piper Fatigue Scale is a scale with 22 numerical items assessing fatigue experienced by the patient. Using a 0–10 numerical scale, the Piper Fatigue Scale measures four dimensions of subjective fatigue: behavioural/severity, affective meaning, sensory and cognitive/mood. The total fatigue score is calculated by adding the four subscale scores and dividing this sum by 4.

Height (in centimetres) was measured using a stadiometer (Seca 22, Hamburg, Germany). Body mass index was calculated as weight (in kilograms) divided by height (in square metres). Waist circumference (in centimetres) was measured twice with a tape measure (Gulick; Creative Health Products, Ann Arbor, MI, USA; range 0–150 cm) at the midpoint between the lower border of the ribs and the upper border of the iliac crest. Both measurements were averaged.

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA). To probe comparability of the groups, Student *t*-tests and chi-square tests were used to examine the differences in baseline socio-demographic and medical features between included patients. A one-way analysis of variance (ANOVA) was conducted to compare the baseline level of study variables.

The main analysis examined whether differences (mean differences) at baseline and eight weeks post treatment existed between hydrotherapy programme and control groups in all outcomes. A 2 × 2 mixed-model repeated-measure analysis of covariance (ANCOVA) with time (pre, post intervention) as the within-subjects variable, intervention (hydrotherapy programme, control group) as the between-subjects variable and age, civil status, educational level, type of hormone therapy, occupational status and clinical features as covariates were used to examine the effects of the intervention on the each study variable. Separate ANCOVAs were done with each outcome as dependent variable. The hypothesis of interest was intervention × time interaction. When an interaction was found, the inter-group effect size was calculated according to Cohen's *d* statistic.[27] An effect size <0.2 reflects a negligible difference, between ≥0.2 and ≤0.5 a small difference, between ≥0.5 and ≤0.8 a moderate difference, and ≥0.8 a large difference.

Results

Sixty-two patients were eligible for pre-screening and 40 (72.5%) were included. All patients underwent axillary lymph node dissection during the surgery. No significant differences in socio-demographic and medical features were found among the 40 patients (72.5%) included and the 22 patients (27.5%) who were excluded or declined to participate, except that a greater number of excluded/declined patients were married (12 (30%) vs. 15 (68.2 %), $P < 0.05$)) (Figure 1). In addition, 12 (30%) participants were taking analgesics (paracetamol) to control increased pain. No patients received any other exercise intervention during the study. There were no differences in age or clinical features between the aquatic exercise and control groups (Table 1), except in employment status, with a higher proportion of non-employed in the control group than in the hydrotherapy group (11 (55%) vs. 5 (25%); $P = 0.044$)).

Adherence to the intervention and adverse events were recorded in a clinical history for each participant after each session. Patients enrolled in the hydrotherapy group completed more than 79% of the 24 physical therapy treatments (mean ± SD number of sessions: 19 ± 3.7), showing a high adherence rate to the programme. Four participants in the hydrotherapy group showed a temporal (1–3 days) increase of pain after one session, but this event did not stop them continuing the programme. No further adverse events were reported.

In comparison to the control group, the experimental group showed a significant increase in pressure pain threshold levels over the cervical point ($F = 14.462$; $P = 0.001$), the shoulder region of the affected side ($F = 4.518$; $P = 0.043$), hand area (affected side: $F = 4.282$; $P = 0.049$; non-affected side: $F = 9.918$; $P = 0.004$) and leg area (affected

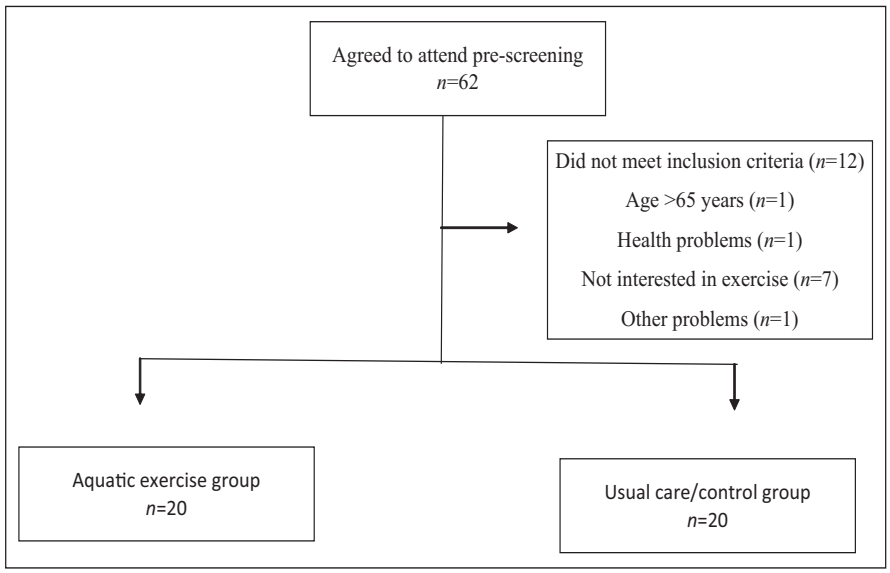

Figure 1. Flow diagram of subject throughout the course of the study.

side: $F = 8.537$; $P = 0.007$; non-affected side: $F = 9.057$; $P = 0.006$). There were no significant group × time × side interactions for pressure pain threshold levels over the shoulder area non-affected side ($F = 3.847$; $P = 0.061$). Neither covariate influenced the results. The hydrotherapy group experienced greater increases in pressure pain threshold levels bilaterally compared with the control group (Table 2). Intergroup effect sizes were large for the cervical area ($d = 1.49$) unaffected hand area ($d = 1.19$) and leg area (affected: $d = 1.30$; unaffected: $d = 1.15$). Intergroup effect sizes were moderate for the affected shoulder area ($d = 0.82$) and hand area (affected: $d = 0.79$; unaffected: $d = 0.76$).

In comparison with the control group, the experimental group did not show a significant improvement in all dimensions of the Piper Fatigue Scale: affective ($F = 0.829$; $P = 0.370$), sensory ($F = 1.476$; $P = 0.234$), cognitive ($F = 0.866$; $P = 0.360$), severity ($F = 0.316$; $P = 0.578$) and total fatigue score ($F = 3.806$; $P = 0.061$) (Table 3).

In comparison with the control group, the experimental group did not show a significant improvement in weight ($F = 0.866$; $P = 0.360$) and body mass index ($F = 0.677$; $P = 0.421$) (Table 4). In comparison with the control group, the experimental group showed a significant change in waist circumference ($F = 6.681$; $P = 0.014$). Neither covariate influenced the results. Pair-wise comparisons revealed a non-significant increase of waist circumference in the control group ($P = 0.246$) compared to a decrease in the aquatic exercise group ($P = 0.016$). Intergroup effect size was moderate for waist circumference ($d = 0.580$).

Discussion

This study confirms that breast cancer survivors with hormone therapy-associated arthralgia demonstrate an improvement in pressure pain threshold and a reduction of waist circumference after eight weeks of hydrotherapy intervention. In addition, a hydrotherapy intervention was well tolerated, with minimal side-effects. No significant benefits were observed in cancer-related fatigue.

To avoid interference with the efficacy of the drug, relief of hormone therapy-associated arthralgia through non-pharmacological strategies is welcomed. We did not find any influence of the type of hormone therapy (tamoxifen vs. aromatase inhibitors) in the analgesic effects of hydrotherapy found in this study. The origin of the arthralgias induced by aromatase inhibitors and

Table 1. Patient characteristics and comparisons between breast cancer survivors

Variable	Control group (n = 20)	Hydrotherapy programme (n = 20)	P-value
Age (years), mean (SD)	46.2 (7.4)	48.4 (10.8)	0.448
Time taking hormone therapy (months)	17.6 (6.9)	18.1 (8.7)	0.876
Civil status, *n* (%)			
Married	11 (55)	12 (60)	0.635
Unmarried	5 (25)	6 (30)	
Divorced	4 (20)	2 (10)	
Educational level, *n* (%)			
Low	7 (35)	4 (20)	0.123
Medium	4 (20)	10 (50)	
University level	9 (45)	6 (30)	
Employment status, *n* (%)			
Home employed	4 (20)	7 (35)	0.044*
Employed	5 (25)	8 (40)	
Non-employed	11 (55)	5 (25)	
Tumour stage, *n* (%)			
I	5 (25)	6 (30)	0.402
II	11 (55)	8 (40)	
IIIA	4 (20)	6 (30)	
Type of surgery, *n* (%)			
Tumorectomy	13 (65)	8 (40)	0.264
Mastectomy	7 (35)	12 (60)	
Type of treatment *n* (%)			
Radiation	0 (0)	2 (10)	0.220
Chemotherapy	1 (5)	0 (0)	
Radiation + chemotherapy	19 (95)	18 (90)	
Hormone therapy			
Tamoxifen	13 (65)	10 (50)	0.557
Aromatase inhibitors			
Anastrozole	2 (10)	3 (15)	
Lestrozole	2 (10)	4 (20)	
Eximestane	3 (15)	3 (15)	
Distribution of joint(s) pain			
Knee/hip	4 (20)	6 (30)	0.427
Wrists/hand/elbow	6 (30)	4 (20)	
Ankle/feet	5 (25)	2 (10)	
Multi-joint diffuse	5 (25)	8 (40)	
Time after surgery treatment (months)	11.15 ± 3.42	15.25 ± 9.00	0.242
Body mass index (kg m^{-2})	26.33 ± 4.42	26.91 ± 6.99	0.784

*P-values for comparisons among group based on chi-square and analysis of variance tests.

tamoxifen is not well known but could be different.[4,6] Possible mechanisms of the analgesic effects of hydrotherapy are well known; the hydrostatic effect of water can alleviate pain by reducing peripheral oedema and sympathetic nervous system activity.[28,29] In addition, we used

Table 2. Pre-intervention, post-intervention and change scores for mean values of pressure pain threshold

Group	Control	Hydrotherapy programme	Between-group differences
Cervical (kPa)			
Pre-intervention	198.99 ± 79.51	212.28 ± 66.65	–105.23 (–162.11; –48.35)*
Post-intervention	162.63 ± 37.99	281.16 ± 65.20	
Within-group change scores	–36.36 (–80.85; 8.12)	68.87 (29.33; 108.41)	
Shoulder, affected side (kPa)			
Pre-intervention	220.99 ± 102.61	233.28 ± 86.19	–56.05 (–110.25; –1.84) *
Post-intervention	219.80 ± 72.69	288.14 ± 58.55	
Within-group change scores	–1.19 (–50.92; 48.53)	54.85 (22.12; 87.58)	
Shoulder, non-affected side (kPa)			
Pre-intervention	194.21 ± 76.87	220.45 ± 68.42	– 48.82 (–99.58; 2.33)
Post-intervention	208.55 ± 83.16	283.41 ± 53.28	
Within-group change scores	14.33 (–32.93; 61.59)	62.95 (32.59; 93.32)	
Hand, affected side (kPa)			
Pre-intervention	241.85 ± 75.09	± 68.85	– 47.42 (–94.52; –0.31)*
Post-intervention	244.41 ± 58.39	297.85 ± 44.06	
Within-group change scores	2.55 (–32.37; 37.48)	49.97 (16.17; 83.78)	
Hand, non-affected side (kPa)			
Pre-intervention	±81.24	223.60 ± 65.84	–77.86 (–128.69; –27.04)*
Post-intervention	233.69 ± 74.62	283.93 ± 57.14	
Within-group change scores	–17.52 (–67.97; 32.92)	60.33 (32.94; 87.72)	
Tibial, affected side (kPa)			
Pre-intervention	41 ± 130.34	323.87 ± 63.44	–116.50 (–198.46; –34.54)*
Post-intervention	322.24 ± 97.26	434.20 ± 73.26	
Within-group change scores	–6.16 (–82.14; 69.81)	110.33 (61,46; 159.20)	
Tibial, non-affected side (kPa)			
Pre-intervention	294.52 ± 88.69	306.10 ± 52.82	–104.61 (–176.07; –33.16)*
Post-intervention	298.55 ± 96.60	414.74 ± 60.43	
Within-group change scores	4.02 (–61.69; 69.74)	108.64 (65.62; 151.66)	

Values are expressed as mean ± standard deviation for pre- and post-intervention data and as mean (95% confidence interval) for within- and between-group changes.
*Significant group × time interaction ($P < 0.05$).

warm-water spa facilities in our study. This can block nociceptors by acting on thermal receptors and mechanoreceptors and exert a positive effect on spinal segmental mechanisms.[30] Pressure algometry cannot tell us whether the reduced pain perception in this study is the result of changes in neuronal excitability or local muscle/joint response, but we can say that the improvement in sensitization process is not influenced by psychological features of the person or mediated by social aspects.[31]

The aquatic exercise programme used in this study failed to improve cancer-related fatigue with respect to usual care. These results are not unexpected, the exercise proposed in this study was focused on the analgesic effect using different mobility exercises combined with stretching and massage procedures. Only 25% of the total time was dedicated to improving the endurance of the patients. It is known that in order to reduce cancer-related fatigue, a large amount of aerobic exercise[32] and moderate resistance programme[33] are needed.

Table 3. Pre-intervention, post-intervention and change scores for mean values of Piper Fatigue Scale

Group	Control	Hydrotherapy programme	Between-group differences
Behavioural/severity			
Pre-intervention	5.82 ± 2.28	4.80 ± 2.19	0.42 (–1.12; 1.97)
Post-intervention	5.66 ± 1.95	4.21 ± 2.59	
Within-group change scores	–0.16 (–1.56; 1.24)	–0.59 (–1.43; 0.26)	
Affective/meaning			
Pre-intervention	6.48 ± 2.25	5.42 ± 2.46	0.64 (–0.80; 2.08)
Post-intervention	6.33 ± 2.27	4.63 ± 2.43	
Within-group change scores	–0.14 (–1.46; 1.17)	–0.79 (–1.56; 0.01)	
Sensory			
Pre-intervention	5.64 ± 2.44	4.71 ± 2.20	0.75 (–0.51; 2.01)
Post-intervention	6.11 ± 2.40	4.42 ± 2.39	
Within-group change scores	0.46 (–0.73; 1.66)	–0.29 (–0.90; 0.32)	
Cognitive/mood			
Pre-intervention	4.86 ± 2.22	4.52 ± 1.49	0.95 (–1.14; 3.04)
Post-intervention	5.81 ± 2.21	4.21± 2.25	
Within-group change scores	0.94 (–0.56; 2.45)	–0.01 (–1.58; 1.56)	
Total fatigue score			
Pre-intervention	5.64 ± 1.87	4.82 ± 1.80	1.08 (–0.05; 2.16)
Post-intervention	6.17 ± 1.94	4.29 ± 2.30	
Within-group change scores	0.55 (–0.55; 1.59)	–0.53 (–1.03; –0.03)	

Values are expressed as mean ± standard deviation for pre- and post-intervention data and as mean (95% confidence interval) for within- and between-group changes.
*Significant group × time interaction ($P < 0.05$).

Table 4. Pre-intervention, post-intervention and change scores for mean values of body composition

Group	Control	Hydrotherapy programme	Between-group differences
Body mass index (kg m^{-2})			
Pre-intervention	26.33 ± 4.42	26.91 ± 6.99	0.23 (–0.35; 0.81)
Post-intervention	26.66 ± 4.57	27.01 ± 7.28	
Within-group change scores	0.33 (–0.06; 0.73)	0.10 (–0.36; 0.55)	
Waist circumference (cm)			
Pre-intervention	86.96 ± 8.79	92.37 ± 19.30	3.70 (0.78; 6.62)*
Post-intervention	87.68 ± 9.49	89.39 ± 18.83	
Within-group change scores	0.72 (–0.56; 2,11)	–2.98 (–5.39; –0.56)	
Weight (kg)			
Pre-intervention	68.86 ± 10.99	69.97 ± 18.69	0.61 (–0.71; 1.93)
Post-intervention	69.61 ± 11.23	70.11 ± 19.17	
Within-group change scores	0.75 (–0.16; 1.66)	0.14 (–0.88; 1.17)	

Values are expressed as mean ± standard deviation for pre- and post-intervention data and as mean (95% confidence interval) for within- and between-group changes.
*Significant group × time interaction ($P < 0.05$).

An interesting finding of this study was the reduction in waist circumference in the hydrotherapy group compared with the control group. These results help to reinforce the evidence level regarding the ability of exercise interventions to reduce waist circumference.[34] However, the intervention failed to improve body size similarly to previous research.[35,36] The increase of physical activity level in the intervention group with respect to the control group ranged from approximately 10.2 MET to 12.2 MET per week.[37,38] This increase in physical activity level associated with a water environment favourable to high levels of energy expenditure with relatively little strain to the body[39] could promote the change in waist circumference found in our sample of breast cancer survivors.

The limitations of our single-institution study were its relatively small sample size and possible selection bias introduced by those who agree to participate in this type of study given the time requirements. In addition, the fact that this was a pragmatic design without randomization process could be considered a limitation of this study, although the observation that there was no significant difference in baseline measurement attenuated the influence of this limitation. The most common approach to pain measurement is through patient self-report scales. These scales include physiological and psychological components that could be difficult to interpret. We decided to assess pressure pain threshold to give a more focused measurement in pain perception. Finally, there are no follow-up data, which could generate doubts about whether the benefit of this programme is sustained.

In conclusion, this report is the first controlled trial establishing the use of hydrotherapy to improve hormone therapy-associated arthralgia. It should be confirmed in a larger randomized trial. Probably in the next years, arthralgia could be a major issue for breast cancer survivors with long-term use of hormone therapy. This study suggests that hydrotherapy could help to attenuate joint pain and improve body composition in breast cancer survivors.

Clinical messages

- Eight weeks of aquatic exercise programme in breast cancer survivors with hormone therapy-induced arthralgia reduce pain threshold.
- Aquatic exercise can contribute to a reduction in waist circumference. However, a programme of 24 treatment sessions carried out in a chest-high pool does not produce significant improvement in cancer-related fatigue, weight or body mass index.

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C

CONCLUSIONES

CONCLUSIONS

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Las SCM presentan un desequilibrio cardiovascular, constatado por un aumento de la frecuencia cardiaca en reposo y niveles más bajos de la VFC, en comparación con las controles sanas. El estudio de la VFC podría ser una herramienta clínicamente útil para detectar enfermedades cardiovasculares. **Artículo I**

De forma similar a lo demostrado en estudios previos en el tejido muscular, las SCM presentan hipersensibilidad neural bilateral y generalizada, además de mostrar una reducción en el rango de movilidad articular durante los test de neurodinamia en el lado afecto comparándolas con las controles sanas. **Artículo II**

Las SCM presentan procesos de sensibilización central determinada por una hiperalgesia bilateral generalizada, que se muestra tanto en el cuello como en la región frontal y dorsal del hombro (inserciones del trapecio superior y del músculo pectoral), en comparación con las controles sanas. **Artículo III**

Un programa de ejercicio acuático de 8 semanas de duración, reduce los umbrales del dolor a la presión y la circunferencia de la cintura en las SCM con artralgia asociada a la terapia hormonal. **Artículo IV**

Conclusión Global

El cáncer y los tratamientos oncológicos provocan en las mujeres SCM importantes efectos secundarios, como desequilibrios cardiovasculares y procesos de sensibilización central. Un programa de fisioterapia acuática se muestra eficaz para reducir el dolor relacionado con el proceso oncológico en mujeres SCM con artralgia asociada a la terapia hormonal.

CONCLUSIONS

BCS show a cardiovascular imbalance, confirmed by an increase in resting heart rate and lower HRV levels compared with healthy controls. HRV study could be a clinically useful tool to detect cardiovascular diseases. **(Paper I)**

Similar to that demonstrated in previous studies in muscular tissue, BCS present bilateral and widespread neural hypersensitivity, furthermore they show a reduction in ROM during ULNTs in the affected side comparing with healthy controls. **(Paper II)**

BCS present central sensitization processes determined by a generalized bilateral hyperalgesia, that it shown both in the neck and the frontal and dorsal shoulder region (upper trapezius and pectoral muscle insertions) compared with healthy controls. **(Paper III)**

Eight weeks of aquatic exercise program reduce pressure pain thresholds and waist circumference in BCS with hormone therapy-associated arthralgia. **(Paper IV)**

Global Conclusion

Cancer and cancer-related treatments cause important side effects, as cardiovascular imbalances and central sensitization processes. An aquatic physiotherapy program proves to be effective to reduce cancer treatment-related pain in BCS with hormone therapy-associated arthralgia.

B

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