UNIVERSIDAD POLITÉCNICA DE MADRID

**FACULTAD DE CIENCIAS DE LA ACTIVIDAD FÍSICA Y
DEL DEPORTE (INEF)**

**Evaluación de los efectos de un programa de actividad física
basado en el trabajo de fuerza en mujeres diagnosticadas de
fibromialgia (FM)**

TESIS DOCTORAL CON MENCIÓN INTERNACIONAL

INTERNATIONAL DOCTORAL THESIS

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Graduada y Máster en Actividad Física y Salud

2019

DEPARTAMENTO DE SALUD Y RENDIMIENTO HUMANO

**FACULTAD DE CIENCIAS DE LA ACTIVIDAD FÍSICA Y DEL DEPORTE
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el trabajo de fuerza en mujeres diagnosticadas de fibromialgia (FM)**

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"Make things as simple as you can, but don't limit yourself to the simple"

(Albert Einstein)

“Haz las cosas lo más simple que puedas, pero no te limites a lo simple”

(Albert Einstein)

AGRADECIMIENTOS

Poner punto y final a este documento no hubiese sido posible sin todas las personas que han contribuido en su desarrollo y sin aquellas que sin su apoyo, insistencia e ilusión me han acompañado en todo el trayecto de esta ardua etapa.

En primer lugar, a la Facultad de Ciencias de la Actividad Física y del Deporte y a la Universidad Politécnica de Madrid por brindarme la oportunidad de desarrollar esta tesis doctoral.

En segundo lugar, a mis directores: *Javier Calderón*, gracias por transmitir siempre la inquietud por el conocimiento y por conocer lo desconocido. Gracias por estar siempre disponible, y por abrirme los ojos en muchas ocasiones ante este marco complejo de realidad.

Javier Rojo, gracias por confiar plenamente en este proyecto desde el primer día. Por haber creído en mí desde el minuto cero sin tener ningún referente. Por apoyarme en los momentos tan duros que este proceso conlleva y por ser el maestro “consejero” no solo en el ámbito académico sino también en el personal. Empezamos a construir este bonito proyecto en septiembre de 2015 y cuatro años después seguimos con la misma ilusión, todo ello gracias al esfuerzo, desempeño y sacrificio depositado en él. Gracias Javier.

A todas las personas que forman el LFE. Me supone un esfuerzo agradecer a este maravilloso equipo ya que un nudo en la garganta impide que pueda redactar estas líneas. Fue difícil pero no imposible formar parte de esta familia trabajadora y luchadora como ninguna otra. Sois un equipo de currantes a la vez que familiar, sois ejemplo de constancia, esfuerzo y superación, sois científicos incansables. Habéis sido mi familia durante estos últimos tres años.

Pedro, gracias de corazón por la confianza depositada, has conseguido que para mí y resto de grupo, que LFE sea además de un grupo de trabajo, una familiar con un objetivo investigador. Ser un líder implica más que solo estar al mando de un grupo de personas y así bien lo demuestras día a día impulsándonos para tener un mejor resultado en los objetivos propuestos. Cierras una etapa como director de un grupo por el que luchas diariamente, por eso y otras muchas cosas más, puedes estar orgulloso. Siempre recordaremos aquella anécdota de “*nuestros inicios nunca fueron buenos...*” pero nuestros finales fueron mejores. Soy afortunada de haberte tenido como director de grupo.

Ana, gracias por estar ahí siempre que lo he necesitado durante estos años. La última fase de la tesis no fue nada fácil y ahí estuviste para apoyarme. Gracias por tus correcciones, consejos y mandatos a orden de la “jefa”. Eres ejemplo de perseverancia.

Roci, compañera de trabajo, de piso y amiga. Hemos compartido muchas emociones en nuestro “pisito”, por nuestros buenos y no tan buenos momentos. Gracias por hacer que mi estancia en Madrid durante estos años haya sido maravillosa. Gracias por incluirme como una más en tu familia. Por cuidarme y mimarme siempre. Estoy segura de que la vida tiene preparada cosas grandes para ti. Eres toda una luchadora.

Miguel, gracias por tener siempre disponibilidad para ayudar en todo lo que necesitamos. Gracias por los momentos de cafés, charlas y risas en el laboratorio. Estoy segura de que pronto conseguirás todo aquello que te has propuesto.

Jabo, nuestro súper técnico y mejor consejero. Gracias por animarme a seguir luchando en este duro camino desde el primer momento. Me has ayudado a creerme el fruto de este bonito proyecto y a ver que el trabajo no lo era “todo” en esta vida. Gracias junto con Anita por compartir planes sociales durante este tiempo.

Lili, eres alma presente de este laboratorio. Coincidimos poco, pero de manera intensa. Gracias por ser ejemplo de constancia y perseverancia. Tus consejos siempre los llevaré en lo más profundo de mi corazón.

Nuri, Laura, Víctor y Bea, permitidme que os agradezca a los cuatro en estas mismas líneas, aunque mis lágrimas impidan que así lo haga. Si en algún momento me hubiesen dicho que iba a tener a compañeros de trabajo tan maravillosos como vosotros, no lo hubiese creído. No puedo estar más orgullosa de teneros en mi trayectoria profesional y por supuesto, en mi vida personal. Sois compañeros de batallas y a la vez de constancia. Sois amor. Gracias de todo corazón por todo lo que hacéis por mí.

Marcos y Benítez. Gracias por compartir vuestra pasión por la lectura, el conocimiento y el saber. Aportáis mucho al LFE.

Especial mención a la Asociación de Fibromialgia de la Comunidad de Madrid. En concreto a nuestra presidenta Luisa, gracias por confiar en este proyecto a pesar de creer en sus inicios que no tenía futuro. Por darme la oportunidad de llevarlo a cabo y por seguir confiando a día de hoy en esta línea de investigación. Especial mención a mis chicas luchadoras, sin vosotras este proyecto no hubiese sido posible. Gracias por vuestra paciencia a lo largo todos estos cuatro años. Recordad que sois ejemplo de superación.

A los Dres. Ciara y Joe, por brindarme la oportunidad de llevar a cabo mi estancia de investigación en Ulster University, la cual se convirtió en una de las mejores experiencias de mi trayectoria profesional. Me llevo 3 meses de mucho trabajo y a la vez de reflexión. Aprovecho esta ocasión para agradecer a dos personas especiales que compartieron conmigo esta experiencia tan dura y entrañable, Fer y María. Fer, eres claro ejemplo que los objetivos se cumplen con trabajo, constancia y muchísima dedicación. Nos propusimos el reto del metaanálisis y tras horas y horas en el campus, así lo

cumplimos. Gracias por estar siempre disponible, por tus intensas correcciones y junto con María, por ser mi apoyo profesional, social y personal durante esta etapa. Gracias por compartir locuras como la de organizar un congreso. De nuevo, gracias a ambos por arroparme en los momentos difíciles.

Agradecer también al Centro de Investigación del Deporte de la Universidad Miguel Hernández (Elche) por acogerme durante los meses de estancia. En especial a Diego y Laura, gracias de corazón por vuestro apoyo en estos 4 meses de trabajo.

Parte de esta tesis va dedicada a una persona especial, mi abuela. Qué difícil era explicarle en qué consistía hacer un doctorado. Me asignó múltiples profesiones, desde profesora de “gimnasia”, de universidad, enfermera, médico... Por desgracia nunca podré explicarle el resultado de este proceso tan sacrificado, nunca podré explicarle el porqué de tantos viajes Crevillente-Madrid-Crevillente durante los tres últimos años de su vida en los que no pude disfrutar de ella como hubiese querido. Abuela, parte de esta tesis va por tí, por enseñarme a que hay que luchar hasta el último momento, a superar obstáculos, caerse, levantarse y seguir corriendo en la misma dirección, siempre con alegría y positivismo. Abuela, allí donde estés, este sacrificio va por ti, por haber sido toda una luchadora igual que lo fui yo durante estos 4 años. Te quiero.

A mis padres, *Jose e Inas* porque gracias a ellos hoy estoy aquí cumpliendo un sueño. Tengo la sensación de que han sido nueve años intensos de continuos cambios, decisiones, traslados, inscripciones, plazos, etc. Y nada de esto hubiese sido posible sin vuestro apoyo incondicional en todo momento. Gracias de corazón por vivir estas etapas de mi vida con la misma intensidad que lo he hecho yo. A ti Papá, decidí tomar el mismo camino que tú, pero diferente especialidad. La pasión por el estudio es algo común que nos une a los dos. Hace 3 años estábamos en tu lectura de tesis y hoy, estamos de nuevo,

pero desde diferente perspectiva. Gracias por sufrir a mi lado, por apoyarme y por confiar en este proyecto que tanto soñé. Eres mi ejemplo de Dr. A ti Mamá, gracias por tu positivismo, por creer en que todo iba a salir bien cuando nada remaba en su dirección, por facilitarme el camino durante estos nueve años y junto con papá, por vuestro apoyo en esta intensa carrera de fondo. Siempre creísteis en que sí podía, aunque mi opinión fuese distinta. Os quiero.

A mi hermana Sandra, gracias por tu apoyo SIEMPRE y junto con Javi, por darme las dos cosas más bonitas e importantes de la vida en los últimos años de esta etapa tan dura y sacrificada. Javier y Alejandro, no tengo palabras para expresar lo tantísimo que os quiero.

Para una persona que, estando siempre ahí, ahora lo está de forma mucho más especial, mi pareja y compañero de vida *Antonio*. Gracias por ayudarme a creerme lo que yo nunca creí, por demostrarme que se puede vivir sin límites y por acompañarme en esta trayectoria llena de caos y lágrimas de felicidad. Gracias por soportar mis crisis, broncas, agobios y horas de encerronas, por compartir horas de flexo, por comprender que el ordenador era mi mejor aliado y, sobre todo, por quererme con virtudes y defectos. Gracias por acompañarme a lo largo de esta trayectoria y vivirlo con la misma intensidad que lo hice yo. Durante casi estos 4 años no ha sido nada fácil nuestra relación, hemos sufrido barreras de presión como estancias, horas de academia, oposiciones, congresos, veranos procesando datos, intervenciones, etc. Hemos estado lejos y a la vez cerca. Porque la gente dice que no se puede y SÍ SE PUEDE. Porque repetiría estos 4 años una y otra vez. Los sueños se cumplen y con personas como tú al lado, todo es más fácil. Y por supuesto, agradecer a tu familia, *Angelines y Antonio*, que hace mucho tiempo se convirtieron en la mía y me han cuidado y apoyado como a una auténtica hija.

Cierro este apartado agradeciendo de todo corazón a mis amigas, que en mayor o menor medida han aportado un granito de arena para que este camino fuese lo más llevadero posible. Gracias por aparecer en mi vida y por vuestro apoyo incondicional en todos y cada uno de los aspectos de mi vida, por nuestras terapias y horas y horas de solucionar el mundo. Mención especial a Carmen, prima y la vez hermana. Gracias por acompañarme en los momentos más duros de mi vida, apoyándome y guiándome hacia el camino correcto. Gracias por ser una parte importante en la historia de mi vida. Te quiero.

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CERTIFICA:

Que la Tesis Doctoral titulada “*Evaluación de los efectos de un programa de actividad física basado en el trabajo de fuerza en mujeres diagnosticadas de fibromialgia (FM)*” que presenta Dña. **CRISTINA ASUNCIÓN MAESTRE CASCALES** al superior juicio del Tribunal que designe la Universidad Politécnica de Madrid, ha sido realizada bajo mi dirección durante los años 2015-2019. El trabajo presentado cumple con todos los criterios científicos y técnicos exigidos, y demuestra la capacidad de su autora para ser merecedora del Título de Doctora con Mención Internacional, siempre y cuando así lo considere el citado Tribunal.

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CERTIFICA:

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Fdo. Fco. Javier Calderón Montero

En 26, a mayo de 2019

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LIST OF ABBREVIATIONS

ACR: American College of Rheumatology
ADL: Activities of Daily Living
AFIBROM: Fibromyalgia Association of the Community of Madrid
BPIQ: Brief Pain Inventory Questionnaire
CK: CreatinKinase
DOMS: Delayed Onset Muscle Soreness
EB: Elastic Bands
EL: External Loads
FD: Function Domain
FIQR: Revised Fibromyalgia Impact Questionnaire
FM: Fibromyalgia
HRQol: Quality of life
LTPAQ: Leisure Time Physical Activity Questionnaire
LPA: Light Physical Activity
Mgb: Myoglobin
MPA: Moderate Physical Activity
NSAIDs: Non-Steroidal Anti-Inflammatories Drugs
OID: Overall Impact Domain
OMNI-GSE: OMNI Global Session in Elderly
PA: Physical Activity
PID: Pain Intensity Domain
PITD: Pain Interference Domain
RM: Maximum repetition
SID: Symptoms Domain
SL: Strength by Self-Loads
SS: Symptom Severity
ST: Sedentary Time
STAI-S: State Anxiety-State Inventory
STP: Strength Training Programs
UPM: Universidad Politécnica de Madrid
VAS: Visual Analogue Scale
WPI: Widespread Pain Index

GRANTED RESEARCH PROJECTS AND FUNDING SUPPORT

The present doctoral thesis is focused on the “*Evaluation of the effects of a strength-based physical activity program on women diagnosed with fibromyalgia*”. The study aimed to develop a quasi- experimental study protocol in order to contribute with valuable data to strength training research in relation to symptomatology, functionality and fibromyalgia impact in women diagnosed with fibromyalgia residing in Region of Madrid (Spain). This study was not funded.

The following institutions collaborated:

1. Laboratory of Exercise Physiology Research Group (LFE). Faculty of Physical Activity and Sport Sciences of *Universidad Politécnica de Madrid* (UPM).
Coordinator: Dr. Pedro José Benito Peinado and Francisco Javier Calderón Montero.
2. Fibromyalgia Association, Region of Madrid, Madrid, Spain. *AFIBROM*.
Responsible: Luisa Fernanda Panadero.

Cristina Maestre Cascales was supported with a pre-doctoral grant by *Universidad Politécnica de Madrid, Convocatoria de contratos predoctorales I+D 2016, en el marco del programa propio de ayudas financiado por la UPM y por el CEI Moncloa*, Spain (RR01/2016). This funding was received to support the doctorate (PhD) program (2015-2019).

Implication of the PhD candidate: Cristina Maestre Cascales was the main researcher for this study under the supervision of Dr. Jesús Javier Rojo González and the Dr. Javier Calderón Montero. She completed all the data collection, directed the intervention program of the study and conducted the data analysis. Finally, the PhD candidate wrote the specific papers included in this doctoral thesis, which are currently

in submission process for different scientific journals. At the present, the muscle-strengthening program in people with fibromyalgia continue to be developed.

The PhD candidate conducted a national research stay at the Training Analysis and Optimization Laboratory, Sports Research Center (SRC), Miguel Hernández University of Elche (UMH) with Dr. Diego Pastor, working on load control in a training program with elderly population. In addition, Cristina participated in another international stay at the University of Ulster in Belfast, United Kingdom with Dr. Ciara Hedges, working on '*Development and Piloting of a Prehabilitation Behavioural Change and Physical Activity Intervention for Fibromyalgia Syndrome*'. This international stay was carried out for the doctorate with international mention.

RESUMEN

Introducción: La fibromialgia (FM) es una enfermedad caracterizada por una sintomatología compleja con presencia de dolor músculo esquelético crónico generalizado junto con otros síntomas incapacitantes. Esta patología supone una elevada carga económica global para los pacientes, generando un problema de salud que conlleva a altas demandas económicas y de atención pública. Las consecuencias de la FM se ven agravadas por un gran número de limitaciones y un estilo de vida sedentario que conducen a una disminución de las capacidades físicas y a un aumento de riesgo de discapacidad. La mayoría de los pacientes afectados por esta patología tienen dificultades para realizar las actividades de la vida diaria, desencadenando en inactividad física. El tratamiento actual para la FM es paliativo, ya que no existe cura. Entre las estrategias utilizadas para aliviar los síntomas físicos y psicológicos y mejorar así la calidad de vida, se encuentra la actividad física. La mayoría de los estudios muestran los efectos del ejercicio físico llevados a cabo a través de programas de entrenamiento aeróbico y acuático en esta patología. A pesar de estas investigaciones, son escasos los estudios que valoran los efectos del entrenamiento de fuerza orientado a las actividades diarias como objetivo principal sobre el dolor, trastornos del sueño, fatiga y ansiedad tratando de especificar la intensidad, volumen y duración apropiada para alcanzar estos beneficios.

Objetivo: En este contexto, el objetivo general de esta tesis doctoral fue valorar los efectos de un programa de fortalecimiento muscular gradual y progresivo orientado a las actividades diarias con el fin de mejorar la sintomatología, funcionalidad física e impacto de la FM para alcanzar una mejor calidad de vida.

Métodos: Este estudio se caracterizó por ser cuasi experimental no aleatorio. El tipo de muestreo fue intencional y se llevó a cabo a través de la asociación de fibromialgia de la

Comunidad de Madrid (AFIBROM). Un total de 41 mujeres participantes formaron parte del estudio cumpliendo los criterios de inclusión. Todas ellas fueron sometidas a un mismo programa de intervención basado en el trabajo de fortalecimiento muscular gradual orientado a las actividades diarias iniciando con trabajo de autocarga, progresando a trabajo de fuerza con material de resistencia, finalizando a pesos libres. Este programa fue dirigido por una graduada en Ciencias del Deporte. La frecuencia de sesiones fue de dos días semanales (no consecutivos) con una duración total de 60 minutos cada sesión. La adherencia al programa fue de un 90%. El programa de intervención abarcó 24 semanas. Las valoraciones se llevaron a cabo una semana antes (pre), mitad de programa (semana 12) y una semana después de finalizar (semana 25). Las variables analizadas fueron: intensidad e interferencia de dolor mediante el Cuestionario Breve de Dolor (CBD), impacto de la FM, función física y sintomatología mediante el Cuestionario Revisado de Impacto de la Fibromialgia (CIFR) y ansiedad estado mediante el Cuestionario de Ansiedad (STAI). La carga interna de las sesiones se controló y estandarizó mediante la escala visual OMNI- GSE específica para población adulta en entrenamiento de fuerza.

Resultados: Se obtuvieron diferencias significativas y elevados efectos clínicos en todos los test de fuerza ($p < 0,002$) y dominios que valoran la calidad de vida, en la semana 12 y al finalizar el programa de intervención (semana 25); función física; $p < 0,001$, impacto general; $p < 0,002$ y sintomatología, $p < 0,003$ (**study I**). El programa de entrenamiento mejoró la condición física ($p < 0,001$) en ambos grupos de edad (menores o igual a 55 y mayores o igual a 56 años). Además, el primer grupo mejoró significativamente las dimensiones del dolor (intensidad del dolor; $p < 0,020$ e interferencia del dolor $p < 0,030$). En cambio, el segundo grupo, no sólo mejoró las dimensiones del dolor (intensidad del dolor; $p < 0,002$ e interferencia del dolor $p < 0,001$), sino que también alcanzó diferencias

significativas en los dominios que valoran la calidad de vida, es decir, la sintomatología, la función física y el impacto general, todas $p < 0,001$. Por otro lado, la capacidad aeróbica (valorada con el test de 2 minutos elevando rodillas) solamente alcanzó asociación inversa significativa con la intensidad del dolor ($p = 0,04$), interferencia del dolor ($p = 0,020$) y el impacto FM ($p = 0,020$) en mujeres jóvenes (**study II**). En relación a los síntomas específicos de la fibromialgia, al finalizar las 24 semanas de intervención, las participantes alcanzaron diferencias significativas en calidad de sueño ($p < 0,05$), hecho que no ocurrió para la ansiedad y fatiga, ambas $p > 0,05$ (**study III**).

Conclusiones: **i)** El programa de fortalecimiento muscular gradual fue efectivo para mejorar la función física, sintomatología e impacto general a las 12 y 24 semanas en mujeres diagnosticadas de FM (**study I**); **ii)** Además, produjo mejorías en la condición física (a nivel de fuerza muscular y capacidad aeróbica) y dolor independientemente del grupo de edad. Sin embargo, la calidad de vida (función física, impacto y síntomas) sólo mejoró en el grupo de mujeres mayores de 56 años. Por otro lado, las mejoras en los niveles de fuerza se asociaron positivamente con la calidad de vida y el dolor en ambos grupos. Sin embargo, las mejoras en la capacidad aeróbica sólo se asociaron con una mayor calidad de vida (función física, impacto y síntomas) y dolor en el grupo de mujeres menores de 55 años. (**study II**); **iii)** El programa fue efectivo para mejorar la condición física, el dolor y la calidad del sueño. A pesar de mejorarlos niveles de la ansiedad y fatiga a las 12 semanas y al finalizar, el programa no fue efectivo para alcanzar diferencias significativas en ninguna de las dos fases (**study III**).

Palabras clave: incapacidad; comportamiento sedentario; fortalecimiento muscular; actividades diarias; dolor; sintomatología; función física.

ABSTRACT

Introduction. Fibromyalgia (FM) is a disease characterized by a complex symptomatology with the presence of generalized chronic musculoskeletal pain the prevailing disabling symptoms. This pathology generates high expenses not only for patients but also for the health care system. The consequences of FM are exacerbated by sedentary lifestyle that leads to a decrease in physical fitness and as a results most of the patients affected by this condition have difficulties in carrying out the activities of daily living which triggers physical inactivity and increased risk of disability. The current treatment for FM is palliative, as there is no healing. Among the strategies to reduce physical and psychological symptoms and thus to improve quality of life is physical activity. Most studies show the effects of physical exercise through aerobic and aquatic training programs on this pathology. Despite this research, few studies assessed the effects of strength training and the adequate combination of intensity, volume and duration aimed at improving daily activities and relieving pain, sleep disorders, fatigue, and anxiety.

Objective: In this context, the main aim of this doctoral thesis was to assess the effects of a gradual muscle strengthening program focused on daily activities in order to improve the symptomatology, physical functionality and impact of FM to achieve a better quality of life.

Methods: A quasi-experimental study was developed. The sampling was intentional and it was carried out in the fibromyalgia association of the Community of Madrid (AFIBROM). A total of 41 participants met the inclusion criteria. All of them, were enrolled in the aforementioned muscle-based intervention program aimed at improving daily activities. This muscle-strengthening program started with self-loads exercise and

it was gradually progressing to strength work by using elastic bands and ending with free weights. A graduate student in Sports Science developed training sessions. The frequency of sessions was two days a week (not consecutive) with a total of 60 minutes/session. Adherence to the program was 90%. The intervention lasted 24 weeks and participants were evaluated in three occasions: one week prior (pre), in the middle (week 12) and one week after finishing the intervention program (week 25). The variables analysed were: pain intensity and pain interference using the Brief Pain Questionnaire (BPQ), FM impact, physical function and symptomatology using the Revised Fibromyalgia Impact Questionnaire (FIQR) and anxiety with the Anxiety Questionnaire Inventory (STAI). The internal load of the sessions was controlled and standardized by the use of OMNI-GSE visual scale specific for adult population in strength training.

Results: Significant differences and high clinical effects were obtained in all strength tests ($p<0.002$) and quality of life dimensions (physical function; $p<0.002$, overall impact; $p<0.002$, and symptomatology, $p<0.003$) at week 12 and 25 (intervention ended) (**study I**). The training program improved physical fitness ($p<0.001$) in both age groups (less than or equal to 55 and greater than or equal to 56 years). In addition, the first group significantly improved pain dimensions (pain intensity; $p<0.020$ and pain interference $p<0.03$). In contrast, the second group, not only improved pain dimensions (pain intensity; $p<0.002$ and pain interference $p<0.001$), but also achieved significant differences in in domains that value quality of life, that is, symptomatology, physical function and overall impact, all $p<0.001$. Moreover, aerobic fitness (assessed with the 2-minute step test) only reached significant inverse association with pain intensity ($p=0.04$), pain interference ($p=0.02$) and FM impact ($p=0.02$) in younger women (**study II**). Regarding the specific symptoms of FM, at the end of 24 weeks intervention, participants reached significant

differences in sleep quality ($p<0.05$), a fact that did not occur for anxiety and fatigue, both $p>0.05$ (**study III**).

Conclusions: **i)** The gradual muscle-strengthening program was effective in improving physical function, symptomatology and FM impact at 12 and 24 weeks in women diagnosed with FM (**study I**); **ii):** This program produced improvements in physical fitness (both at the level of muscle strength and at the aerobic level) and pain regardless of age group. However, quality of life (physical function, impact and symptoms) only improved only in the group of women over 56 years of age. Moreover, improvements in aerobic fitness are only associated with increased quality of life (physical function, impact and symptoms) and pain in the group of women under the age of 55. (**study II**); **iii)** In addition, this program was effective in improving physical fitness (upper and lower limb strength, lower limb flexibility, and aerobic fitness), pain, and sleep quality. Despite improvement levels of anxiety and fatigue at 12 weeks and at the end of the muscle strengthening program (week 25). This was not effective in achieving significant differences in either phase (**study III**).

Key words: disability; sedentary behavior; muscle strengthening; daily activities; pain; symptomatology; physical function.

I. INTRODUCTION

I.1. CHARACTERISTICS OF FIBROMYALGIA

Fibromyalgia is a chronic disease, characterised by a variegated clinical picture (Gerwin, 2013). Until recently, it was a rather under-recognised entity, and some clinicians even doubted its actual existence. However, since 2010 the American College of Rheumatologists (ACR) has provided clear diagnostic criteria that can help clinicians to recognise this disease (Segura-Jiménez *et al.*, 2014; Triñanes *et al.*, 2014) and treat patients accordingly. One of the most important features is generalised pain that severely influences the quality of life. Moreover, these patients can also present with insomnia, depressive symptoms, gastrointestinal disturbances, etc.

I.1.1 Definition

Fibromyalgia is a chronic disease characterized by widespread musculoskeletal pain as the main symptom, associated with the presence of multiple locations of tender points (Wolfe *et al.*, 1990). Chronic widespread pain is defined as pain for at least three months in both sides of the body, both above and below the waist (Wolfe *et al.*, 1990, 1995). This disease has been considered as a disorder regulation of unknown aetiology (Sarzi-Puttini *et al.*, 2008), characterized by increased sensitivity to painful stimuli (hyperalgesia) and lowered pain threshold (allodynia) (Staud and Domingo, 2001). However, fibromyalgia has recently been defined as a complex dimensional disorder with pain as main symptom (Wolfe *et al.*, 2013) associated with others of similar importance, such as fatigue, non-restorative sleep, mood alterations, stiffness, cognitive problems, depression, anxiety and poor health-related quality of life (HRQoL) (Silverman *et al.*, 2010; Segura-Jimenez *et al.*, 2015a; Wolfe, 2015).

1.1.2 Evolution of knowledge

Over the past 20 years, research in the clinical field as well as the neurophysiological basis for this disorder has been increasing. The clinical concept of FM was initially mentioned by Yunus *et al.*, (1981) in the publication of 1990 American College of Rheumatology (ACR) criteria for the FM classification (Wolfe *et al.*, 1990). An evolution of the clinical understanding of FM over the last two decades has emphasized the importance of symptoms beyond pain. In this context, it was necessary to establish criteria for a correct diagnosis.

Therefore, the new definition of FM affirms that symptoms are not an all-or-nothing with the possibility of presenting with varying severity (Wolfe *et al.*, 2011). The research setting has provided clinical specialists with the confidence to acknowledge a condition that presents with only subjective symptoms and no objective clinical findings (Perrot, Dickenson and Bennett, 2008). Furthermore, dysregulation of pain processing has been shown at various levels in the nervous system, but we still lack an objective test in the clinical setting to confirm a diagnosis or gauge response to treatments (Yunus, 1983; Perrot, Dickenson and Bennett, 2008).

The clinical challenge of this condition remains as there so that is still no objective clinical finding or test to confirm the diagnosis, or to assess the severity of physical and psychological symptoms. This has generated controversy and clinical uncertainty, and a diagnosis of FM is often only considered when other diagnostic possibilities have been excluded (Ghazan-Shahi, Towheed and Hopman, 2012). This insecurity by health care professionals may be a factor leading to frequent use of unnecessary investigations and can contribute to excessive medicalization of patients. It has been clearly documented

that a definite diagnosis of FM leads to reduced health care use and better global patient health (White *et al.*, 2002b; Hughes *et al.*, 2006).

In summary, FM is a constant struggle for different reasons. This disease usually has a burden that negatively impacts on people's daily living (Fontaine, Conn and Clauw, 2010; Goes *et al.*, 2012; Segura-Jimenez *et al.*, 2015a; Costa *et al.*, 2017). People with fibromyalgia often require more resources from the health care system which leads to a burden on the economy (Sicras-Mainar *et al.*, 2009). Given that the signs of FM are invisible (e.g., pain, fatigue and depression), society often has negative responses to people with FM by, for instance, accusation of malingering, disbelieving, and lack of understanding (Kool *et al.*, 2009, 2013; Cameron *et al.*, 2018). The condition leads to controversy for researchers and clinicians, as the predisposing, triggering, and perpetuating factors related to FM and its symptoms are not consensually determined as yet (Clauw, 2014).

This paucity of knowledge may be, at least, in part responsible for the lack of a treatment that universally, uniformly, and relevantly helps to reduce the impact of the disease long-term (Macfarlane *et al.*, 2017).

1.1.2 Epidemiology

The prevalence of fibromyalgia varies from 0.5 to 5% depending on the country (White and Harth, 2001). In Spain, approximately 2.4% of the general population over 20 years old are affected (Mas *et al.*, 2008). In absolute numbers, this means that 70,000 patients are affected by FM in our country. The percentage of people affected in the Community of Madrid is 5% (Ramos, 2017).

By sex, approximately 4.2% of women suffer from disorder, whereas only 0.2% of men are affected, which is a female: male ratio of 21:1 (Mas *et al.*, 2008). Regarding

the distribution in age groups, FM appears in all age groups, with a maximum prevalence between 40-50 years (4.9%), while it is relatively infrequent in people over 80 years of age (Mas *et al.*, 2008; Marques *et al.*, 2017). Due to the low number of diagnosed fibromyalgia in men, research has mainly been focused on women, somewhat ignoring the study of fibromyalgia in men.

Researchers affirm that the percentage of affected individuals can vary according to the level of academic achievement, with the prevalence in the uneducated population being 4.8%, 3% with primary education and 0.6% with university education. Social class is also inversely related to prevalence, in that people active employment have a lower prevalence (32.7%) than the rest of the population (52.3%) (Mas *et al.*, 2008).

1.1.4 Diagnosis and symptomatology: fibromyalgia is more than just pain

Fibromyalgia is present in a heterogeneous population; i.e., the clinical picture is highly variable among people (Alvarez-Gallardo *et al.*, 2017a). Even within a person, symptoms of FM usually fluctuate daily (Finan *et al.*, 2011; Vincent, Whipple and Rhudy, 2016). Initially, FM was considered to be a condition of pain, and this concept was reinforced by the ACR criteria in 1990 which only included a) widespread pain for at least 3 months, b) tenderness measured by a physical examination with the presence of 11 of 18 tender points $\leq 4 \text{ kg/cm}^2$ (Wolfe *et al.*, 1990). This ACR classification criteria created a crude definition of fibromyalgia as widespread pain by imposing the presence of 11 tender points (Wolfe *et al.*, 2010). As time passed, objections to the 1990 ACR criteria developed, with the bases that the presence of different tender points cannot be an objective assessment of whole body pain (Salaffi and Sarzi-Puttini, 2012). Furthermore, digital palpation instead of algometry is the most widely used method among examiners (Fitzcharles and Boulos, 2003). Without an objective instrument, the application of an

equal pressure of 4 kg is therefore doubtful (Fitzcharles and Boulos, 2003; Salaffi and Sarzi-Puttini, 2012). In addition, FM has been recognized as a disease that is related to pain and non-pain symptoms (Wolfe *et al.*, 2014, 2016).

Today, the understanding of FM acknowledges that patients with FM have complex physical and psychological symptoms characterized by more than pain, presenting with other complaints present of variable intensity, such as fatigue, stiffness, depression and cognitive problems among others (Silverman *et al.*, 2010; Wolfe *et al.*, 2013). Accordingly, an updated version of the diagnostic criteria had been proposed by Wolfe *et al.* (2010) and Salaffi and Sarzi-Puttini (2012).

Later, the ACR published in 2010 the following preliminary criteria, emphasizing that they do not correlate with functional impairment. The diagnostic criteria are composed by two dimensions: a) Widespread Pain Index (WPI) as measure of the number of painful body regions, with the patients being asked to indicate in which of 19 body areas, they had pain during the week before. The minimum total score of WPI is 0 and the maximum total score is 19, b) The Symptom Severity (SS) score is a measure of symptomatology where the patients are asked to indicate the severity of fatigue, trouble thinking or remembering and waking up tired (unrefreshed) over the previous week; and to answer whether (or not) they have had pain or craps in the lower abdomen, depression or headache during the previous 6 months. The minimum total score of SS is 0 and the maximum total score is 12. This preliminary diagnostic criteria establish 3 conditions: i) $WPI \geq 7$, and $SS \geq 5$, or WPI between 3-6 and $SS \geq 9$; ii) Symptoms have been present at similar level for at least 3 months; and iii) The patients do not have a disorder that would otherwise explain the pain.

Figure 1. Distribution of trigger points in fibromyalgia (Villanueva Cerdá, Monsalve, Bayona, De Andrés, 2004).

Besides those mentioned above, other symptoms or associated conditions include restless legs syndrome, periodic limb movements in sleep, multiple chemical sensitivity and interstitial cystitis (Yunus, 2007a, 2007b). Each of these symptoms plays a variable role in the presentation of an individual patient and all contribute to a greater or lesser degree towards the overall effect of impaired quality of life and reduced functional activity.

All diagnostic criteria for FM include a compulsory presence of chronic pain (Wolfe *et al.*, 1990, 2014). It is assumed that hyperactivity of the central nervous system is a key player in processing stimuli that are usually not painful as painful (Lannersten and Kosek, 2010; Woolf, 2011). Researchers affirm that the concept of central sensitization is caused by different phenomena's such as the activation of painful pathways without an apparent stimulus causing the "non-nociceptive pain", due to the stimulation of fibers that lead to these painful sensations. That is, it is defined as an

anomaly in the perception of pain, so that stimuli that are usually not painful are perceived as painful (Plazier *et al.*, 2015).

The 2010/2011 ACR criteria correctly classify more than 87.033% of the cases that also met the previous criteria (ACR-1990) (Wolfe *et al.*, 1990). These criteria are a simple way of evaluating FM patients and allow for easier understanding and management of the pathology. However, the 1990 ACR criteria remain those accepted by the scientific community for the correct diagnosis of FM (Moyano, Kilstein and Alegre de Miguel, 2015). Moreover, the use of these criteria (ACR, 2010) (Wolfe *et al.*, 2010) is much discussed by rheumatologists, since it dispenses with physical examination and does not take into account any complementary study.

These 2010/2011 criteria generated disagreement regarding the erroneous classification of a small fraction of patients who did not present generalized pain (Egloff *et al.*, 2015). Misclassification occurs because the WPI, while indicating the number of painful sites, does not consider the spatial distribution of the sites. This problem can be obviated by imposing the requirement of meeting a widespread pain criterion, such as the 1990 criterion. However, the 1990 widespread pain criterion is often very restrictive (Wolfe, Egloff and Häuser, 2016). Therefore, the proposed criteria modifications now require the presence of what we have called “generalized pain,” to distinguish it from the 1990 definition of widespread pain.

An important consequence of this change is that one previous criterion for diagnosis, WPI of 3–6 and SSS ≥ 9 is not entirely correct since is now impossible to satisfy our modification with a WPI < 4. The proposed generalized pain criterion is easier to use than the 1990 widespread pain, as it requires only a quick look by the clinician to decide if the patient meets the criterion. In the current (2016) revision of the criteria these areas

and headache and facial pain should not be included in the quadrant or region definition of generalized pain (Wolfe *et al.*, 2016).

FM may now be diagnosed in adults when all of the following criteria are met: (a) Generalized pain, defined as pain in at least 4 of 5 regions, is present, (b) Symptoms have been present at a similar level for at least 3 months, (c) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 or WPI of 4–6 and SSS score ≥ 9 , (d) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically important illnesses (Wolfe *et al.*, 2016). Despite all this, there is no specific test for the diagnosis of FM, due to the fact that complementary explorations in these patients are intended to rule out the existence of other pathologies.

FM patients can experience important cognitive dysfunction, which is associated with pain, but not current depression or anxiety, and includes poor working memory, spatial memory alterations, free recall, and verbal fluency (Park *et al.*, 2001; Cánovas *et al.*, 2009; Rodríguez-Andreu *et al.*, 2009). Cognitive symptoms are present in FM even after adjusting data for age, medications, education, and depression (Cánovas *et al.*, 2009). However, cognitive changes were no different when compared to other pain patients, suggesting that pain may affect cognition (Walitt *et al.*, 2008). Although most patients experience associated symptoms to varying degrees, they are not a requirement for a diagnosis of FM.

FM may accompany other medical, neurological, or rheumatologic illnesses as a comorbid condition (Goldenberg, 2009). Conditions that have been associated with FM include amongst others various rheumatologic conditions such as systemic lupus, erythematosus and rheumatoid arthritis, as well as neurologic disorders such as multiple

sclerosis and post-polio syndrome (Trojan and Cashman, 1995; Goldenberg, 2009). It is important to appreciate that FM can coexist with these conditions in order to do a treatment appropriately. For example, a continuous complaint of pain due to FM in a patient with rheumatoid arthritis would be incorrectly treated by increasing treatments with disease modifying agents, rather than addressing the symptoms associated with FM (Plesner and Vaegter, 2018).

I.1.5 Treatment for fibromyalgia

Current evidence indicates that there is no unique ideal treatment that responds to the symptomatology of patients with FM, but there is a wide range of effective pharmacological (Sumpton and Moulin, 2008), cognitive behavioral (Castel *et al.*, 2012) and exercise-based interventions (Mannerkorpi and Henriksson, 2007; Goldenberg, 2008) and psychological-educative programs (Mannerkorpi and Henriksson, 2007; Castel *et al.*, 2012).

The **pharmacological treatment** is often used and among the most common are analgesics, non-steroidal anti-inflammatories, opioids and psychotropic drugs (Sumpton and Moulin, 2008; Fitzcharles, Ste-Marie and Pereira, 2013). Nutritional supplements are also commonly used (Tavoni *et al.*, 1987; Jacobsen, Danneskiold-samsøe and Andersen, 1991; Pate *et al.*, 1995). However, these treatments produce little benefit for the patient.

Medications should be used to complement a broad multidisciplinary program to address the treatment of fibromyalgia. The goal of treatment should be to achieve symptomatic relief, not the actual elimination of such symptoms. Patients should be fully informed of the various existing treatment modalities and should be able to freely adjust their own therapeutic plans, within reason. In these patients, polypharmacy is very common, and it should be avoided since it does not produce beneficial results. In addition,

all medication must be re-evaluated periodically, adjusting the dose in order to justify its continued use (Russell, 1996; Leventhal, 1999).

However, success in pharmacological treatment can be achieved if patients start with very low doses, increasing the dose until the desired therapeutic effect is achieved, or unacceptable side effects appear. According to **alternative medicines**, the mind-body exercise (which incorporates human biological and psychological aspects into treatment, with the intent of using the mind to affect physical functioning and promote health (Taggart *et al.*, 2003; Wang *et al.*, 2018) and relaxation therapies can increase pain tolerance in fibromyalgia patients (Carbonell-Baeza *et al.*, 2010; Carson *et al.*, 2010; Carbonell-Baeza *et al.*, 2011). Recently, there has been an increase in complementary and alternative modalities for managing fibromyalgia (some examples include: Tai-Chi, Biodanza, Yoga, breathing exercises) (Busch *et al.*, 2007; Rahman, Underwood and Carnes, 2014). These new approaches, with limited applicability not having scientific evidence, have been proposed in the last seven years (De Silva *et al.*, 2010; Oliveira *et al.*, 2017) so will require further investigation.

Evidence from the literature indicates that **non-pharmacological therapies**, particularly Physical Activity (PA) gradually and progressive of moderate intensity (Macfarlane *et al.*, 2016, 2017; Gavilán-Carrera *et al.*, 2018), provides the best outcomes for the treatment of fibromyalgia. This type of intervention must be incorporated into the treatment plan for each patient, as it has been shown to improve the psychological components of fibromyalgia, symptomatology and physical function (Busch *et al.*, 2008, 2013b; Busch, Webber, Brachaniec, Bidonde, Dal Bello-Haas, *et al.*, 2011; Nüesch *et al.*, 2012; Mist, Firestone and Jones, 2013; Bidonde, Busch, *et al.*, 2014; Bidonde, Busch, *et al.*, 2014b; Soriano-Maldonado, Ruiz, *et al.*, 2015; Cordoba-Torrecilla *et al.*, 2016; Jones, 2016; Bidonde, Busch, Schachter, Overend, Kim, Goes, *et al.*, 2017).

There is persuasive evidence that also induces positive changes in the brain areas associated with pain processing (Flodin *et al.*, 2015; Ellingson *et al.*, 2016). These findings raise the prospect that movement may be ‘disease modifying’ or at least affects key underlying physiologic perturbations. Recommending exercise in a clinic setting remains more of an ‘art’ than a ‘science’. Prescription of PA should be specific and targeted to the type of symptoms that these patients present (Jones, 2016b).

Figure 2. Classification of the different treatments applied to fibromyalgia.

Although there are several treatment options available, the optimal management for FM remains elusive. Clinical guidelines recommend a broad range of pharmacological and non-pharmacological therapies (Carville *et al.*, 2007; Häuser, Thieme and Turk, 2010). Nevertheless, there is evidence that physical exercise can have an impact on the clinical presentation of patients with FM. Indeed, exercise is considered to be the main non-pharmacological strategy in the management of FM.

I.2 QUALITY OF LIFE: AGING AND FUNCTIONAL LIMITATIONS IN FIBROMYALGIA PATIENTS

In general, not dependent on FM, as a result of the aging process, the efficacy of various physiological functions begins to decrease slightly until it becomes more evident at about 55 years of age (Pate *et al.*, 1995). Sarcopenia as consequence of the ageing process is associated with functional loss and disability and, as a consequence, poor quality of life and increased mortality (Doherty, 2003). The mechanism that explains the process of sarcopenia approaches that the decrease in muscle mass is associated with a decrease in muscle strength, which in turn decreases physical performance, limiting the performance of the usual activities of daily life, increasing disability and dependence (Koca *et al.*, 2016). From the age of 55, the slow decline in muscle mass and strength accelerates sharply, especially in sedentary people (Hughes *et al.*, 2002).

The consequences of FM are exacerbated by a host of comorbidities and a sedentary lifestyle leading to declines in physical abilities, functional impairments, and increased risk for disabilities (Clauw and Crofford, 2003; Mannerkorpi, Svantesson and Broberg, 2006; Bennett *et al.*, 2007a) leading to decreased levels of muscular strength and muscular resistance (Vandervoort, 2001). Patients with FM have functional limitations that are more debilitating or equal to those shown by persons with

osteoarthritis or rheumatoid arthritis (Hawley and Wolfe, 1991). They also demonstrate alterations in motor control associated with an increased risk of falls (Costa *et al.*, 2017). Furthermore, in people with FM (White *et al.*, 1999; Wolfe and Michaud, 2004), loss of function has been strongly associated with work disability.

Patients with FM need more time to complete activities of daily living (ADL) (walking and stair-climbing) and report more exertion compared to healthy volunteers (Huijnen *et al.*, 2015). It might be that the muscle recruitment pattern of patients with FM is altered resulting in a less efficient performance during daily activities. Therefore, these patients will need more energy to perform regular ADL (Vlaeyen and Linton, 2000), producing higher levels of fatigue in their daily life (Huijnen *et al.*, 2015).

Current evidence shows an association between physical fitness and symptoms of FM. According to Jones *et al.* (2008), reduced physical function is associated with pain intensity and fatigue in individuals with FM. Assumpcao *et al.* (2010) found certain association between pain intensity, pain threshold, and symptoms of FM, with muscular strength and dynamic balance. Also, changes in pain threshold and symptoms of FM could be caused by the effect of muscle strength and flexibility exercise, as the improvement in muscle strength, flexibility and dynamic balance produced a positive impact on overall pain. Since the evidence on physical exercise has been associated with a strong improvement in symptoms, a better knowledge of the relationship between physical function and severity of symptoms of FM is necessary in order to determine causality, as well as to design a guide for effective therapies.

The functional limitations produce a considerable impact on daily activities and quality of life. FM patients experience severe consequences on family environment due

to functional limitations, economic status, etc. In addition, the FM is often associated with constant changes in employment and job losses (Collado *et al.*, 2014).

It is therefore not surprising that FM shows a negative effect on the quality of life of affected patients (Wolfe *et al.*, 1997; Epstein *et al.*, 1999; Raphael *et al.*, 2004) as well as their relatives and spouses due to associated physical and psychological disorders (Tutoglu *et al.*, 2014). The ability to work can be considered an important aspect of quality of life. For patients with fibromyalgia, work is a way to contribute to society and meet other people, although it may present a burden when the symptoms of this disease affect the performance of job tasks, housework, and relationships with co-workers, among others (Palstam and Mannerkorpi, 2017; Amorós-Molina and Berlanga-Fernández, 2018).

Currently we find many sedentary work activities that involve little PA, such as spending many hours sitting, either in front of a computer, driving or attending a business. These aspects worsen the neuromuscular condition of the patient, which further aggravates the symptoms of fibromyalgia (Cathey, Wolfe and Kleinheksel, 1988; Collado *et al.*, 2014; Segura-Jimenez *et al.*, 2015b; Thieme *et al.*, 2015). Literature has shown that the majority of women presenting FM exhibit muscular desynchronization, being more susceptible to muscle damage with activity (Henriksson *et al.*, 1982; Bengtsson *et al.*, 1986; Panton *et al.*, 2006). Some authors have also found that one third of the women diagnosed with FM did not have the upper-body strength (force-generating capacity of a muscle) to carry out simple routine activities such as reaching high shelves or washing their hair (Wolfe *et al.*, 1990). Muscle strengthening exercise is an essential component of fitness, which refers an individual's ability to have the physical requirements for work and daily activities (Da *et al.*, 2000; Costa *et al.*, 2017).

1.3. PHYSICAL FITNESS IN FIBROMYALGIA PATIENTS

Levels of physical fitness (specifically, aerobic fitness and muscle strength) are powerful predictors of morbidity and mortality among in the general population (Blair *et al.*, 1989; Barry *et al.*, 2014) regardless of PA (Lee *et al.*, 2011; Eisenlohr-Moul *et al.*, 2015), age, smoking, adiposity, and other disease risk factors (Lee *et al.*, 2010). In fact, it is suggested that FM may have a larger impact on physical health rather than on psychological health (Segura-Jimenez *et al.*, 2015a). Among the physical impairments of FM patients, low levels of strength, endurance, flexibility, and poor balance are extremely relevant (Aparicio *et al.*, 2015; Muto *et al.*, 2015).

Theoretically, an association between fitness levels and pain can be expected based on modulating influences of the autonomic nervous system: low physical fitness may result in unbalanced autonomic nervous system function, which can impact on pain (Light *et al.*, 2009) or alternatively, pain may lead to a reduction in fitness, which brings about an unbalanced autonomic nervous system function (Geenen, Jacobs and Bijlsma, 2009).

Current evidence shows that the improvement of the already mentioned different components of the physical fitness are associated with lower levels of pain (de Bruijn *et al.*, 2011; Soriano-Maldonado *et al.*, 2015b), lower FM severity (Soriano-Maldonado, Henriksen, Segura-Jimenez, *et al.*, 2015; Collado-Mateo *et al.*, 2016) and better health-related quality of life (Carbonell-Baeza *et al.*, 2013; Soriano-Maldonado, Henriksen, Segura-Jimenez, *et al.*, 2015; Collado-Mateo *et al.*, 2016; Sener *et al.*, 2016). In addition, Aparicio *et al.* (2011, 2013b, 2015) suggested that physical fitness might be useful as a complementary tool in the diagnosis and monitoring of fibromyalgia (specially the

handgrip strength and 6 -min walk tests). Therefore, physical fitness might be considered a relevant health marker in people with fibromyalgia.

In this context, it is of clinical interest to provide standard reference values of different components of physical fitness using easy-to-use, inexpensive, feasible and reliable assessment tools for their quantification. The Senior Fitness Test battery (Rikli and Jones, 1999a,b) is a set of field-based tests widely used in patients with fibromyalgia Carbonell-Baeza *et al.*, 2011; Cherry *et al.*, 2012; Aparicio *et al.*, 2013; Carbonell-Baeza *et al.*, 2015; Jones *et al.*, 2015; Soriano-Maldonado, Ruiz, *et al.*, 2015; Cordoba-Torrecilla *et al.*, 2016; Soriano-Maldonado *et al.*, 2016; Alvarez-Gallardo *et al.*, 2017b; Ofei-Dodoo *et al.*, 2018). Thus, it can be considered a feasible and reliable test to assess physical fitness in this population (Carbonell-Baeza *et al.*, 2015).

1.4 THE APPROACH TO PHYSICAL ACTIVITY IN FIBROMYALGIA.

Physical inactivity is one of the major public health problems of the 21st century (Blair, 2009) and several longitudinal studies have shown the negative consequences on health by leading a sedentary lifestyle (Thorp *et al.*, 2011; Katzmarzyk and Lee, 2012; Matthews *et al.*, 2012).

Several symptoms and functional limitations in daily life have been strongly associated with chronic pain, including deficient energy and muscular discomfort, physical mobility limitations, lifting groceries, climbing stairs and stooping (Björnsdóttir, Jónsson and Valdimarsdóttir, 2013). Moreover, female but not male, with chronic pain tend to refrain from PA (Björnsdóttir, Jónsson and Valdimarsdóttir, 2013). Pain-related fear in the fibromyalgia populations limits voluntary PA (Turk, Robinson and Burwinkle, 2004), and leads to fibromyalgia patients mostly spending their time in sedentary (Turk, Robinson and Burwinkle, 2004; Ruiz *et al.*, 2013).

Women with FM who are physically active seem to manage their ability to modulate pain better than those who are less active (McLoughlin, Stegner and Cook, 2011). It has also been suggested that peripheral mechanisms, such as abnormalities in microcirculatory capillaries (Morf *et al.*, 2004), irregularities in mitochondria (Castro-Marrero *et al.*, 2013) and alteration of muscle oxygen utilization (Shang *et al.*, 2012) might reduce peripheral tissue oxygenation and have an important role in central sensitization. In this context, an increase of tissue oxygenation following exercise could reduce peripheral and central sensitization and, consequently, reduce clinical pain (Hooten *et al.*, 2012).

Fibromyalgia patients can benefit from PA to maintain or improve their health (Busch, Webber, Brachaniec, Bidonde, Bello-Haas, *et al.*, 2011). International organizations support the use of PA-based interventions as a complementary tool in the therapeutic armamentarium against fibromyalgia (Brosseau, Wells, Tugwell, Egan, Wilson, Dubouloz, Casimiro, Robinson, McGowan and Busch, 2008). Fibromyalgia patients with active lifestyle patterns show greater physical function and lower levels of pain than those who tend to be physically inactive (Kop *et al.*, 2005; Fontaine, Conn and Clauw, 2010). This knowledge suggests the existence of a cyclic relation between PA and fibromyalgia symptoms (McLoughlin *et al.*, 2011). Despite the known benefits of PA on their symptomatology, fibromyalgia women are usually less physically active than control groups (McLoughlin *et al.*, 2011). Fibromyalgia patients decrease their PA levels due to fear of pain (Turk, Robinson and Burwinkle, 2004; Enlander, 2013; Nijs *et al.*, 2013) which will cause a worsening of symptom followed by higher levels of inactivity.

1.4.1 Strength training on symptomatology in FM patients

Exercise has been largely considered as a key component in a comprehensive treatment program for people with FM (Burckhardt, Clark and Bennett, 1993). The potential adverse effects of exercise depend on the level of exercise in relation to the participant's level of conditioning and age (Gearhart *et al.*, 2008; Cortez *et al.*, 2015). There is scientific evidence on the effects found following aerobic training programs (Nichols and Glenn, 1994; Wigers, Stiles and Vogel, 1996; van Santen *et al.*, 2002; Valim *et al.*, 2003; Ayan *et al.*, 2007; Günendi, Meray and Özdem, 2008; Thomas and Blotman, 2010; Sañudo *et al.*, 2010; Arcos-Carmona *et al.*, 2011; Hooten *et al.*, 2012; Cullinane *et al.*, 2014; Bardal, Roeleveld and Mork, 2015; Garcia-Hermoso, Saavedra and Escalante, 2015; Bidonde *et al.*, 2017), aquatic programs (Jespersen *et al.*, 2003; Gusi *et al.*, 2006; Tomas-Carus *et al.*, 2007; Bidonde, Busch, *et al.*, 2014), flexibility programs (Jones *et al.*, 2002; Matsutani, Assumpção and Marques, 2012) and those combined with others physical qualities (Jones *et al.*, 2000, 2002; Bircan *et al.*, 2008; Sevimli *et al.*, 2015) and also multicomponent programs (Hooten *et al.*, 2012). Several researchers studies have reported that strength training showed improvements in pain (Jones *et al.*, 2002; Valkeinen *et al.*, 2006; Figueroa *et al.*, 2007; Bircan *et al.*, 2008; Hooten *et al.*, 2012; Gavi *et al.*, 2014; Larsson *et al.*, 2015), physical function (Kingsley *et al.*, 2005; Valkeinen *et al.*, 2008; Gavi *et al.*, 2014; Palstam *et al.*, 2016), and sleep quality (Bircan *et al.*, 2008; Ericsson *et al.*, 2016; Andrade, Vilarino and Bevilacqua, 2017) , in addition to improvement in the quality of life of these patients.

In terms of emotional factors, it has been studied that low levels of well-being are clearly associated with the severity of fibromyalgia, fatigue, and pain (van Middendorp *et al.*, 2010; Estévez-López *et al.*, 2017). Previous studies suggest that women with fibromyalgia who present higher levels of strength achieved higher levels of subjective

well-being, specifically higher levels of positive affection and life satisfaction, as well as lower levels of negative affection (Maestre-Cascales *et al.*, 2019). Therefore, physical exercise programs that improve strength levels may not only provide physical but also psychological (i.e., higher levels of subjective well-being) benefits for women with fibromyalgia.

Most of the research related to physical exercise and FM has been done with the aim of improving the cardiorespiratory levels of patients. The idea of using strength training programs (STP) to relieve symptomatology is recent and was overlooked since it was believed that FM was directly caused by muscle trauma (Clark, Jones, Burckhardt and Bennett, 2001). Current research has shown that the etiology of FM may not be muscular, and therefore strength training may be beneficial. Fatigue is one of the first symptoms of FM (Geel and Robergs, 2002) and it is perceived at rest, during and after exercise, as well as days after exercise is restarted (Nørregaard *et al.*, 1994; Bendtsen *et al.*, 1997). In the first few seconds of exercise, the energy metabolism that takes the main contribution is phosphines, and it has been suggested that this metabolism is altered in people with FM (Geel and Robergs, 2002). Some authors (Geel and Robergs, 2002) showed that using STP, through exercises involving the body's most important muscle groups can normalize and reduce the amount of fatigue associated with exercise in people with FM (Bircan *et al.*, 2008; Ericsson *et al.*, 2016).

Muscle pain is the predominant symptom in people with FM (Karper, Hopewell and Hodge, 2001). Increases in myoglobin (Mgb) and creatine kinase (CK) are associated with muscle damage and pain (Nørregaard *et al.*, 1994). Studies that have investigated plasma Mgb and CK concentrations before and after exercise found no significant differences between people with FM compared to the controls group. These data suggest that although muscle pain is present, it may not be due to muscle damage (Bidonde,

Angela Jean Busch, *et al.*, 2014a). However, studies that have used strength training programs have found that so-called delayed onset muscle soreness (DOMS) is clearly evident in people with FM (Clark, Jones, Burckhardt and Bennett, 2001; Karper, Hopewell and Hodge, 2001; Hakkinen *et al.*, 2002). This delayed pain is the acute effect of predominantly eccentric training (Sherman, 1992; Folland *et al.*, 2001). In the case of FM patients, it is suggested that the key to optimal strength training is the reduction of eccentric exercise and the inclusion of pauses at the end of each movement, which may help to avoid the appearance of some of these DOMS experienced by FM patients (Sherman, 1992; Clark, Jones, Burckhardt and Bennett, 2001).

Several studies have examined the effect of STP on the symptoms of patients with FM, however these studies have been conducted over short periods of time, generating discordance in the results obtained (Nichols and Glenn, 1994; Häkkinen *et al.*, 2001; Bircan *et al.*, 2008a; Hooten *et al.*, 2012; Gavi *et al.*, 2014; Roman, Campos and Garcia-Pinillos, 2015; Andrade, Vilarino and Bevilacqua, 2017). However, the influence of ST in a progressive and long-lasting approach oriented to the daily activities on pain intensity and interference, anxiety state, impact disease, physical function, fatigue, and sleep quality has not been investigated deeply.

Since STP for the treatment of FM for the treatment of FM patients' symptoms, studies detailing exercise protocols are needed. The current study presents a possibly treatment option that can be used to alleviate the patient's symptoms by altering daily activities to improve the patient's quality of life. In clinical practice, the use of ST is feasible and requires few resources. Starting strength training programs at light intensities and then progressing to moderate, moderate-high intensities can help alleviate symptoms and provide global health benefits (Maestre-Cascales, Peinado Lozano and Rojo González, 2019).

MAIN EXPECTED CONTRIBUTION OF THIS THESIS

Gradual intervention programs based on muscle strengthening exercise and oriented towards ADL are needed in order to reduce the loss of functional ability, improve physical, psychological symptoms and the impact of fibromyalgia. The vast majority of the studies including training programs in FM people are focused on aerobic, flexibility, and combined exercise. So, there is little literature about gradual strength exercise on daily activities, being a major limitation in fibromyalgia patients. Regarding methodology, a 24- week's strength training program focused on daily activities with gradual and progressive intensity was applied. Moreover, the current study compared the different phases to assess the evolution of fitness, physical and psychological symptoms and FM impact. Therefore, we aim to contribute to the advancement of knowledge about the effects of a gradual muscle strengthening program (24 weeks) oriented to the ADL on the quality of life in people diagnosed with fibromyalgia.

II.HYPOTHESIS AND OBJECTIVES

II.1 HYPOTHESIS AND OBJECTIVES

The symptomatology, functionality, impact and severity of fibromyalgia can be improved through physical activity programs. People diagnosed with fibromyalgia present a sedentary lifestyle due to limitations caused by this disease. As a consequence of incapacity, fitness levels are low, in particular, muscle performance is impaired. Therefore, the main aim of this PhD. thesis was to contribute to the knowledge regarding the effect of gradual muscle strengthening program on quality of life in FM population. This PhD. thesis was composed by 3 sequential studies that represent the subsections of this thesis.

GENERAL HYPOTHESIS

Hypothesis: A gradual muscle strengthening program can improve symptoms, physical function, and overall impact in women diagnosed with FM.

GENERAL OBJECTIVE

Objective: To analyse the effects of a 24-week gradual muscle strengthening program oriented to daily activities on the symptomatology, physical function and overall impact in women diagnosed with FM residents in the Region of Madrid.

Hypothesis and objectives of Study I

Hypothesis: A gradual muscle strengthening program will increase strength levels and physical function decreasing overall symptoms and the impact of FM significantly in women diagnosed with FM.

Objective: To analyze the evolution of physical fitness (upper and lower limb), symptomatology, physical function and overall impact throughout the 24 weeks of a gradual muscle strengthening program.

Hypothesis and objectives of Study II

Hypothesis 1: A gradual muscle strengthening program will significantly increase fitness regardless of age. However, the group over 56 years of age will benefit most at the end of the program in their quality of life (physical function, symptoms, and impact) by attenuating the effects of sarcopenia that do not impact so heavily on women under 55 years of age.

Hypothesis 2: Strength-related fitness tests will show association with quality of life and pain as it has been suggested in the literature a gain in strength levels will improve these symptoms.

Objective 1: To evaluate the effects of strength training on physical fitness, pain, and quality of life (symptoms, physical function, and overall impact) in women with FM establishing a cut-off point on the basis of the beginning of the aging and muscle decline.

Objective 2: To determine the association between physical fitness and pain, impact, physical function, and symptomatology in both age groups.

Hypothesis and objectives of Study III

Hypothesis: A gradual muscle strengthening program will significantly improve anxiety, sleep quality, fatigue, pain intensity, and pain interference in women diagnosed with FM.

Objective: To examine the effect of a 24-weeks gradual muscle strengthening program oriented to daily activities on sleep quality, fatigue, pain domains, physical function and anxiety state in women diagnosed with FM.

III. MATERIAL AND METHODS

As mentioned before, the present PhD. thesis correspond to the intervention program (24 weeks) carried out in first person in collaboration with the Association of FM, Region of Madrid (AFIBROM). Figure 3 shows the timeline of all tasks performed during the 4 years of the doctoral program in relation to the present study.

Throughout this chapter, all materials and methods used to develop the publications related to this intervention program are detailed.

Figure 3. Timeline process for all task developed in this doctoral thesis.

III.1 DESIGN:

The studies were quasi-experimental uncontrolled trial with 24 weeks of intervention without control group. Data collection took place at three moments; **(i)** in week 0, before starting the intervention (January 2016); **(ii)** in week 12, midway through the intervention programme (April 2016); and **(iii)** week 25, at the end of the intervention (June 2016). The programme, as mentioned above, lasted 24 weeks, starting in week 1 and ending in week 24. The study was conducted in Madrid. Table 1 provides an overview of the timeline of this methodology and table 2 provides an overview of the methods of each study elaborated the PhD. thesis.

Regarding to the intervention program, from 21 March to 3 April (two weeks intervention) coincided with holiday's period. Therefore, in order to maintain the adherence of the participants, a special program of exercises was designed specifying: the methodology of work (being the same as in previous face-to-face sessions), the intensity, recovery intervals, exercises for the activation and relaxation phase, and specific exercises belonging to the elastic bands phase (**APPENDIX IV**).

Also, at the end of this period (week 25), a program was designed with all the characteristics worked during the 24 weeks of intervention; phases of exercise, intensity, series, recovery period, exercise intervals, in order to maintain adherence during summer holidays and to be able to incorporate again in September for the following course (**APPENDIX V**).

Table 1. Timeline of data collection and the intervention program.

2016*					
JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE
1-3	1-7	1-6	4-10	2-8	6-12
18-24 Pre-data collection (i) Week 0	8-14	7-13	11-17 Middle-data collection (ii) Week 12	9-15	13-19
25-31 Pre-data collection (i) Week 0	15-21	14-20	18-24	16-22	20-26 End intervention Week 24
18-24 Start intervention Week 1	22-28	21-27 CATHOLIC HOLIDAYS	25-1	23-29	27-30 Post-data collection (iii) Week 25
25-31	29	28-3 CATHOLIC HOLIDAYS		30-5	

* The months are divided into weeks, from Monday to Sunday.

Table 2. Summary of doctoral thesis methods.

Study	Design ^a	Sample ^a	Main variables studied	Instruments
I	Quasi-experimental (week 0 VS week 12 VS week 25)	41 FM cases	Physical function, FM impact, symptomatology, total score FIQR, physical fitness (upper and lower limb strength in dominant and non-dominant side).	FIQR domains, OMNI GSE scale, fitness test arm curl and handgrip in dominant and non-dominant plus 30-s chair stand).
II	Quasi-experimental (week 0 VS week 25)	17 FM $\leq$ 55 years, 24 FM $\geq$ 56 years	Pain intensity, pain interference, physical function, impact FM, symptomatology, physical fitness (upper and lower limb strength in dominant and non-dominant side, and handgrip strength).	FIQR, BPIQ, OMNI-GSE scale, fitness tests (arm curl, 30-s chair stand, 2-minute step and handgrip strength)
III	Quasi-experimental (week 0 VS week 12 VS week 25)	41 FM cases	Pain intensity, pain interference, physical function (upper and lower limb strength, and flexibility), anxiety state, fatigue, and sleep quality.	FIQR, BPIQ, OMNI-GSE, scale, STAI-S fitness tests (sit and stand, arm curl, 30-s chair stand and 2-minute step).

ACR, American College Rheumatology fibromyalgia diagnostic criteria modified in 2010; BPIQ, Brief Pain Inventory Questionnaire; FIQR, Revised Fibromyalgia Impact Questionnaire; RCT, Randomised Controlled Trials; SWLS, Satisfaction with Life Scale; MMSE, Mini Mental State Examination; OMNI-GSE, OMNI Global Session in Elderly; STAI-S, State Anxiety-State Inventory.

^a All the participants were women.

III.2 PARTICIPANTS

The study began with 55 women, of whom 14 participants withdrew from the study for different reasons (25%): 6 (11%) not meeting inclusion criteria, 4 (7%) other reasons, 3 (5%) incorporation to work due to medical discharge, 1 (2%) injuries due to a work accident. Finally, a total of 41 women with FM participated in the study. All of them were recruited by the FM association, Region of Madrid, AFIBROM (Spain) and were chosen using convenience sampling, that is, they were selected according to their availability and willingness to participate in the study. Figure 4 shows the participants who completed the study.

Figure 4. Consolidated standards of reporting trials flow diagram.

The inclusion criteria for people with fibromyalgia were: a) Women aged between 20 and 75 years old; b) Diagnosed with FM by a rheumatologist and meeting the American College of Rheumatology (ACR) criteria on examination according to the criteria of the American College of Rheumatology (Wolfe *et al.*, 1990); c) no physical disabilities; d) report no physical activity practise or a maximum of 1 weekly session, and e) able to communicate effectively with the study staff. Participants were excluded if they a) are male; b) disease that could be exacerbated by the practice of physical activity, such as cancer or heart disease; c) are in a gestational state; and d) change from usual care therapies during the intervention period.

III.3 ETHICAL CONSIDERATIONS

The Ethics Committee of the Universidad Politécnica de Madrid (Madrid, Spain) approved the studies of the current PhD. Tesis research project. The ethical guidelines of the Declaration of Helsinki (modified in 2000) were followed for all studies and all participants provided written informed consent before taking part in the studies (**APPENDIX III**).

III.4 PROCEDURE

Firstly, the fibromyalgia association of the community of Madrid was contacted to show them the design of the project and the importance of getting participants interested in participating in it (**APPENDIX I**). Then, all members of AFIBROM were informed via e-mail about the project to be carried out. Those interested attended a face-to-face meeting at the association where all formal aspects of the intervention were presented (training program contents, objectives, measurements, inclusion/exclusion criteria, etc.) (**APPENDIX II**). It was also mentioned that they would be subjected to a series of tests (non-invasive) and questionnaires at different during the program. Then,

members interested in participating signed the informed consent and then filled out the sociodemographic questionnaire (related to personal and disease information). Once the questionnaires were collected, participants who did not meet the inclusion criteria were excluded. Measurements were performed on three different time points, as mentioned in the study design by the same researcher in order to reduce inter-examiners error. The first time point (week 0), the two weeks prior to the start of the intervention, baseline measurements were carried out, establishing a rigorous order in the protocol. First of all, the Revised Fibromyalgia Impact Questionnaire (FIQR), the Brief Pain Inventory Questionnaire (BPIQ), the State Anxiety Inventory (STAI-S), were completed. Then, the anthropometric measurements were assessed and finally, the Senior Fitness Test battery and dynamometry were used to evaluate physical fitness. For the second time point (week 12) and the third (week 25) the same evaluation protocol that was used that in week 0 was repeated.

III.5 INSTRUMENTS

QUESTIONNAIRES OUTCOMES

Sociodemographic and clinical data

The participants filled out an initial questionnaire designed by the researchers that included questions about gender, age, marital status, educational level, current occupational status, and time since diagnosis, drugs, therapies, years of onset of symptoms, year of diagnosis, pain-sensitive points, level of pain on a Visual Analogue Scale (VAS) of 0-100 and presence/absence of acute or terminal illness (such as cancer, stroke, recent cardiomyopathy, severe coronary disease, schizophrenia, or any other disabling injury).

The Revised Fibromyalgia Impact Questionnaire (FIQR)

The FIQR is a self-administered questionnaire, comprising 21 individual questions with a rating scale of 0 to 10. The questions compose 3 different domains; function (FD), overall impact (OID) and symptoms (SD) score (ranging 0-30, 0-20 and 0-50 respectively (Bennett *et al.*, 2009). The FIQR total score range from 0 to 100, with a higher score indicating greater effect of the condition on the person's life. We used the Symptom Impact Questionnaire with control participants. The SIQR (Friend and Bennett, 2011) is a slightly modified version of the FIQR used with non-fibromyalgia patients. Number of questions, domains and scoring is the same as the FIQR. We used the Spanish version (Salgueiro *et al.*, 2013).

The Brief Pain Inventory (BPI)

The BPI is a validated self-report measure of pain (Cleeland and Ryan, 1994) in two domains. Firstly, pain intensity/ severity domain (PID) through 4 items, and second, pain interference on daily functions domain, encompassing 7 items with a recovery period of the last 24 h (PITD). Both domains are scored with a numerical rating scale of 0-10 (0 pain and no interference, 10 pain is as bad as you can imagine and completely interfere) and were calculated as the mean of the element responses in each of both domains. The BPI has been used extensively in fibromyalgia studies (Arnold *et al.*, 2005; Bennett *et al.*, 2007a; Chappell *et al.*, 2008; Russell *et al.*, 2008; Mease *et al.*, 2011; Williams and Arnold, 2011). The pain intensity/severity domain was used to represent the symptom domain of pain.

The State Anxiety Inventory (STAI-S)

The STAI-S was used to assess the level current anxiety-state (Anxiety-S). This is a 20-item self-administered scale of current feelings “at this moment”: 1) not at all, 2) somewhat, 3) moderately so, and 4) very much so, using items that measure subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system. The range of score is 20-80, with higher indicating a greater level of anxiety (White *et al.*, 2002a; Spielberger *et al.*, 2017) .

The effort perception scale OMNI-GSE (Silva-Grigoletto *et al.*, 2013)

The OMNI-GSE scale was used to control and standardize the overall internal load based on which participants were asked to choose a score that reflected their perceived degree of effort previously, during and after training. The range is through VAS of 0-10 with the help of faces that represent the effort, with 0; being extremely easy and 10; extremely hard. This was developed to be used in collective classes (intermittent) with adult populations.

Figure 5. Participants filling the sociodemographic questionnaire.

CLINICAL MEASURES

Anthropometry and body composition

We used a portable eight-polar tactile-electrode impedanciometer (InBody R20, Biospace, Seoul, Korea) to measure body weight (kg), body fat (kg and %), skeletal muscle mass (kg) and Body Mass Index (%) (BMI). This last measurement was made at least two hours after the last lunch, with participants released from clothing and metal objects and having remained standing at least five min before the assessment. Following the manufacturer's recommendations, we asked them not to have a shower, not to practice intense physical exercise, and not to ingest large amounts of fluid in the hour before the measurement. The validity and reliability of this instrument are adequate (Malavolti *et al.*, 2003; Segura-Jimenez *et al.*, 2014).

Height (cm) was measured using a stadiometer (Seca 22, Hamburg, Germany). The waist and hip circumference (cm) was measured with the participant standing up. For the waist, the midpoint between the ribs and the crest of the ileum was used as a reference. And for the hip, the most prominent part of the gluteus above the symphysis pubis was used as a reference (Holtain Ltd) (Cruz, Armesilla and de Lucas, 2009).

Figure 6. Waist circumference measurement.

PHYSIOLOGICAL MEASURES

Blood Pressure and Heart Rate (HR) were evaluated at rest with a tensiometer (Omron PL-100 Pro Logic, United Kingdom) and a fingertip pulse oximeter (Beurer PO-30, Ulm, Germany) was used to measure oxygen saturation and it also showed the pulse rate.

Figure 7. Oxygen saturation and resting pulse

Figure 8. Blood Pressure and Heart Rate measurements with Omron PL-100 Pro Logic, United Kingdom.

PHYSICAL FITNESS TESTING

The Functional Senior Test battery was used because it is relatively easy to administer, safe, and requires minimal equipment and space (Rikli and Jones, 2013). It has shown no ceiling and floor effects, which is a relevant aspect for this study due to the heterogeneity of fibromyalgia patients (Wilson, Robinson and Turk, 2009). Therefore, the tests used are feasible to perform in clinical and community settings, and psychometric properties of these tests are adequate (Aparicio *et al.*, 2015; Carbonell-Baeza *et al.*, 2015). Furthermore, we also used the handgrip strength test which is commonly used when evaluating fibromyalgia patients (Carbonell-Baeza *et al.*, 2011). The main functional capacity components studied were:

Lower-body muscular strength

- The “**30-s chair-stand test**” involves counting the number of times within 30 seconds that an individual can rise to a full stand from a seated position with back straight and feet flat on the floor, without pushing off with the arms. The arms were crossed at the chest level (Rikli and Jones, 1999). Higher scores indicate better performance.

Figure 9. 30-seconds chair-stand test.

- The **handgrip** strength test is valid, reliable and feasible (Nordenskiöld and Grimby, 1993; Valkeinen *et al.*, 2008) as it provides useful information about the participant's overall muscle strength. It was evaluated using a TKK hand dynamometer as the systemic bias is small and has been shown to have the most reliable results when repeated measurements with known weights are used. The grip range is adjustable, using the formula suggested by Ruiz *et al.* (2006) to calculate the optimal grip distance: $y = x/5 + 1.5$; “x” being the hand size, and “y” the grip length. The participant squeezed gradually maintaining at least 2 seconds, performing the test with the right and left hand in turn. Each patient made two attempts with each hand, with the arm fully extended, forming an of 30° angle with respect to the trunk (Ruiz-Ruiz *et al.*, 2002). The maximum score in kilograms (kg) for each hand was recorded. For analysis, the mean score of the

left and right hand or as independent variables, dominant side and non-dominant side was used. Higher scores indicate better performance.

Figure 10. Handgrip strength test with dynamometer TKK.

Upper-body muscular strength

- The “**arm curl test**” which measures the number of times that, with the person seated, a hand weight (for women 2 kg or 1 kg if the test was adapted) can be curled through full range of motion within 30 seconds (Rikli and Jones, 1999). Patients performed one trial with both hands. For the analysis, the mean score of the left and right hand or as independent variables, dominant arm and non-dominant arm was used. Higher scores indicate better performance.

Figure 11. Arm curl test in resting position.

Figure 12. Arm curl test in maximum flexion.

Lower body flexibility

- The “**box sit-and-rich**” test involves sitting on the floor with legs stretched out straight ahead. Shoes should be removed. The soles of the feet are placed flat against the box. Both knees should be locked and pressed flat to the floor - the tester may assist by holding them down. With the palms facing downwards, and the hands-on top of each other or side by side, the participant reaches forward along the measuring line as far as possible. Ensure that the hands remain at the same level, none reaching further forward than the other. After some practice reaches, the participant reaches out and holds that position for a one-two seconds while the distance is recorded. Two attempts were recorded, collecting the best score achieved. Higher scores indicate a better performance.

Figure 13. Box sit-and-rich test.

Aerobic fitness

- The “**2-minute step test**” requires that the participant to walk in place, lifting her knees to an intermediate point between her kneecap and the iliac crest. Participants could use a wall or chair to maintain balance, if necessary. This test consists of completing cycles (1 cycle is 2 knee lifts, one with each leg) for two minutes. A higher step count indicates better cardiovascular fitness. The participants were asked to perform as fast as they could, keeping in mind their functional limitations. Higher scores indicate a better performance.

Figure 14. 2-minute step test.

Figure 15. Instruments applied in this current study.

TRAINING PROGRAM

The program consisted of 24 weeks of supervised muscle strengthening in a group setting, progressively increasing in intensity (according to patient's tolerance), and transferable to the actions of daily life with exercise performed in the standing, sitting, and lying positions, in order to improve their physical fitness, in particular overall strength (Bircan *et al.*, 2008a). The frequency was two days a week with a duration of 60 minutes for each session. Volume and intensity were controlled throughout the program as described below (figure 5). The intensity was controlled by means of the OMNI - Global Session in the Elderly Scale (OMNI-GSE) (Silva-Grigoletto *et al.*, 2013) used in inexperienced people or in elderly populations, taking into account their incidence at the functional level (Gearhart *et al.*, 2009; Guidetti *et al.*, 2011; Colado *et al.*, 2012). Also, heart rate monitoring was performed by using a pulse oximeter (Beurer PO-30, Ulm, Germany) at the beginning, middle, and the end of each session.

The program included three different phases of progressive exercise in volume and intensity (Busch *et al.*, 2013a; Jones, 2016b). **1st phase (SL)** (*five weeks*): strength by self-loads including balance, coordination, and postural control. The intensity of effort was between 3-4 of the OMNI-GSE scale; **2nd phase (EB)** (*seven weeks*): elastic bands were included as resistance material along with the content of the first phase. The intensity was between 4-5 of OMNI-GSE scale, and **3rd phase (EL)** (*twelve weeks*): external loads together with the contents of the previous phases. The intensity was between 6-8 of OMNI-GSE scale.

The first 10 minutes of the session were devoted to joint mobility and movement. Then, 40 minutes of strength exercise including balance, coordination, and postural control and finally, 10 minutes of stretching and relaxation. The dynamic exercise was

through circuits. Each session covered two different circuits (six exercises each). Two series per circuit were performed in each session (Sanudo *et al.*, 2011). The initial work time was 30 seconds per exercise, increasing 5 seconds every two weeks until the participant reaches one minute of work per exercise (week 14). For the last 10 weeks the working time was kept at 1 minute. Recovery time was 30 seconds between exercise, 2-min between series and 5-min between circuits. At the beginning of the session an explanation/ demonstration of each exercise was provided in order to reduce the possibility of harmful movements.

In the 3rd phase, the load was set at a level that patients could easily manage. However, as in previous studies (Van Santen *et al.*, 2002; Kingsley *et al.*, 2005; Gearhart *et al.*, 2008; Sanudo *et al.*, 2011), during the course of this phase the level gradually increased according to the patient's tolerance, the individual knowledge of the symptoms and the level of general fatigue. At the beginning, during and end of every sessions the pulse and oxygen saturation was measured by oximeter as a safety precaution, as some participants presented feeling of fatigue or drowning during the exercise. The OMNI-GSE scale previously mentioned was administered.

The evolution of the load in this third phase, from week 13 to the end, week 24, depended on the characteristics of the participants (Sanudo *et al.*, 2011). The progression of the absolute load in the main muscle groups was from 0.2 to 2.0 for upper limb. Specifically, back work out ranged from 0.5 to 5.0, and finally, for lower limb the load varied from 1.5 to 3.0.

Figure 16. Intervention protocol based on strength training oriented to daily activities.

Figure 17. Strength training exercises in each protocol phase.

RESULTS are presented below for each contribution that constitutes the present doctoral thesis