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Multicomponent exercise program and functional capacity in institutionalized frail and cognitive impairment nonagerians

Doctoral thesis

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“A un niño le lleva un año adquirir el movimiento independiente, y diez años adquirir movilidad independiente. Una persona mayor puede perder ambas en un solo día”

Bernard Isaacs, “The Challenge of Geriatric Medicine”, 1992

LIST OF PUBLICATIONS:

This doctoral thesis is a compendium of the following publications:

Review Article- Casas- Herrero A, Izquierdo M. Physical exercise as an efficient intervention in frail elderly persons. An Sist Sanit Navar 2012 Jan-Apr; 35(1): 69-85. (Impact Factor: 0.31)

Experimental studies:

- Study I: Casas-Herrero A, Cadore E, Zambon –Ferraresi *et al*. Functional capacity, muscle fat infiltration, power output and cognitive impairment in institutionalized frail oldest old. Rejuvenation Res 2013. Jul 3 (Impact factor: 2.91)

- Study II: Cadore E, Casas Herrero A, Zambon-Ferraresi F *et al.* . Multicomponent exercises including muscle power training enhance muscle mass, power output and functional outcomes in institucionalized frail nonagerians. Age (Dordr). 2013 Sep 13. (Impact factor: 3.94)

- Study III: Eduardo L. Cadore, Ana B. Bays Moneo, Marta Martinez Mensat, Andrea Rozas Muñoz, Alvaro Casas-Herrero Leocadio Rodriguez-Mañas, Mikel Izquierdo. Positive effects of resistance training in frail elderly patients with dementia after long-term physical restraint. Submitted

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ABSTRACT

Frailty is an age-associated syndrome characterized by decreases in the functional reserve and resistance to stressors due to changes in several physiological systems. Frailty is increasingly recognized as a highly prevalent entity that is distinct from disability and comorbidity and that increases the vulnerability of older adults to clinically important outcomes, including functional decline, falls, and institutionalization. One of the cornerstone issues underlying frailty syndrome is sarcopenia (aging-induced loss of muscle mass, strength and muscle function) that is exacerbated by decreased physical activity, causing a decline in overall function and leading to frailty. The diagnosis of frailty includes physical impairments, such as low gait speed, fatigue, decreased physical activity and low grip strength. Along with sarcopenia, skeletal muscle fat infiltration, which is assessed through muscle tissue attenuation, is associated with an increased risk of mobility loss in older men and women.

Skeletal muscle power decreases earlier than muscle strength with advancing age. Muscle power seems to be more closely associated with performance on functional tests than muscle strength in elderly populations. This loss of power is directly associated with a reduction in mobility and in the ability of performance basic or instrumental daily living activities. Measures of muscle strength should be accompanied of other measurements knowledge as functional capacity measurements. They are very useful in the assessment of frailty and frequently are related with mobility (i.e. gait velocity, Time up and Go, grip strength). Knowledge about the relationships between skeletal muscle power, strength, mass, and functional capacity could improve the exercise recommendations for this population.

Mild cognitive impairment (MCI) is seen as a transitional state between normal cognitive aging and early dementia. Cognitive impairment has been closely related to frailty because both diseases share some pathophysiological mechanisms and short-term and mid-term consequences (e.g., hospitalization, incidence of falls, disability, institutionalization, and death). It is well known that people with dementia exhibit some of the symptoms of the frailty phenotype such as a low gait velocity and a low level of physical activity, but the presence of similarities of differences in the physical outcomes in the frail elderly with or without cognitive impairment has not been

studied. These differences could be particularly evident during the dual-task gait paradigm.

Dementia is a syndrome that represents a major public health problem because it impacts the capacity for daily living activities and impairs social and occupational functions. With the progression of dementia, elderly individuals with cognitive disorders generally become frail, disabled and frequently institutionalized patients. One of the major negative consequences of dementia is the severe decline in physical activity, which can be attributed to several causes, including the use of physical restraints to prevent falls. The restraints are associated with adverse social, physical and psychological outcomes, such as loss of freedom and autonomy, humiliation, incontinence, demoralization, depression, aggression, exacerbated sarcopenia, loss of strength, impaired ability to stand and walk and overall decreased functional status and quality of life. The frailty syndrome may accelerate the trajectory of decline in patients with dementia.

Due to the physical domains that are related to frailty, physical activity is one of the most important components in the prevention and treatment of this syndrome. Previous studies shows that multicomponent exercise programs, and especially resistance exercise, are the most relevant interventions to slow down disability and other adverse outcomes related with frailty. Nevertheless, only a small number focused on institutionalised very old frail participants and the majorities were designed with short-term resistance training programs. The benefits of a multicomponent exercise program that includes muscle power loading and balance and functional capacity stimulus in frail nonagenarians remain to be fully investigated. Indeed, data on the effects of exercise programs on muscle size and muscle fat infiltration are scarce. Exercise intervention (e.g., resistance, walking and balance training), which is designed to improve the physical domains of frailty, may also benefit elderly patients with dementia. Additionally, physical exercise, such as endurance and resistance training, has been shown to improve cognitive function in subjects with dementia. However, to the best of our knowledge, no study has investigated the effects of exercise intervention in frail subjects with dementia after long-term physical restraint and little is known about the regressive effects of training cessation in frail elderly patients with dementia once the training intervention has ended.

To investigate the above mentioned issues, the present Thesis was composed by the following studies and respective purposes. In the Review article: to look through the previous literature showing exercise as an effective intervention in frail elderly persons; Study I: To examine the neuromuscular and functional performance differences between frail oldest old with and without MCI; Study II: To investigate the effects of multicomponent training on muscle power output, mass and muscle tissue attenuation, the risk of falls and functional outcomes in frail nonagenarians; Study III: To investigate the effects of an 8-week multicomponent exercise intervention on muscle strength, incidence of falls and functional outcomes in frail elderly patients with dementia after long-term physical restraint, followed by 12 and 24 weeks of training cessation.

In the review article main features of the frailty syndrome and functional test for diagnosis were revised. Main characteristics of the resistance training and its components in frail elderly were analyzed. Other types of training were reviewed and finally it was revised the effect of training in other domains of the frailty spectrum as falls, cognitive decline and depression. In the Study I, forty-three elderly men and women (91.9±4.1 years) were classified into three groups: the frail group, the frail with MCI group (frail +MCI), and the non-frail group. Strength tests were performed for upper and lower limbs. Functional tests included 5-meter habitual gait, time-up-and-go (TUG), dual task performance, balance and rise from chair ability. Incidence of falls was assessed using questionnaires. The thigh muscle mass and attenuation were assessed using computed tomography. In the study II, twenty-four elderly (91.9±4.1 years old) were randomised into intervention (muticomponent exercise) or control group. In both groups, before and after intervention strength and power tests, gait velocity and TUG tests with and without dual task paradigm were performed. Balance was assessed using the FICSIT-4 tests (Frailty and Injuries: Cooperative Studies of Intervention Techniques). The ability to rise from a chair test was assessed, and data on the incidence and risk of falls were assessed using questionnaires. Functional status was assessed before measurements with the Barthel index. Midthigh lower extremity muscle mass and muscle fat infiltration were assessed using computed tomography. In the study III, twenty-four frail elderly patients with dementia (88.1 ± 5.1 years) were recluted. Strength tests were performed Gait velocity and TUG tests were performed basal and using dual taske paradigm. Balance and the ability to rise from a chair were also assessed. Functional status was assessed using the Barthel Index, and the Mini-Mental State Examination (MMSE) was used to measure general cognitive function. The incidence of falls was also examined.

The main findings of the review article were that multicomponent exercise programs, and especially resistance exercise are the most relevant interventions in the previous literature to slow down disability and other adverse outcomes related with the frailty syndrome. Indeed, these programs are valuable interventions in other frailty domains such as falls, cognitive decline and depression. In the study I, the main finding observed was that frail oldest old with and without MCI have similar functional and neuromuscular outcomes. Furthermore, the functional outcomes and incidences of falls are associated with muscle mass, strength, and power in the frail elderly population. The primary result of the study II result was the significant improve observed in the intervention group in the TUG with single and dual tasks, rise from a chair and balance performance and the reduction of the incidence of falls. The intervention group showed enhanced muscle power and strength. Moreover, there were significant increases in the total and high-density muscle cross-sectional area in the intervention group. The control group significantly reduced strength and functional outcomes. The main result of the study III was the absence of difference after the first 4 weeks of training in the majority of functional outcomes. There were no changes observed in the 5-m gait velocity test, the TUG, in dual-task performance or in the number of rises from a chair, whereas a significant improvement was observed in balance tests. However, after the second part of the training period, the intervention group required significantly less time for the TUG test and measures of the isometric hand grip, hip flexion and knee extension strength and leg press 1RM improved. A significant reduction was also observed in the incidence of falls. After 24 weeks of training cessation, abrupt decreases were observed in nearly all of the physical outcomes.

The conclusions of the present Doctoral Thesis were that: (I) Multicomponent exercise programs are efficient strategies to prevent disability and other frailty domains such falls, cognitive decline and depression in frail aged patients. However, it is necessary to explore optimal resistance training components and develop specific clinical guides of physical activity for this target population (Review article). (II) Frail oldest old with and without MCI share functional and neuromuscular outcomes (Study

I). (III) Routine multicomponent exercise intervention should be prescribed to frail nonagenarians because overall physical outcomes are improved in this population. (Study II). (IV) Systematic multicomponent exercise intervention improved muscle strength, balance and gait ability in frail elderly patients with dementia, even after long-term physical restraint, and these benefits were lost after training cessation (Study III).

RESUMEN

La fragilidad es un síndrome asociado al envejecimiento que se caracteriza por un deterioro en la reserva funcional y en la resistencia a estresores debido a cambios que afectan a varios aparatos y sistemas. En la actualidad es reconocida como una entidad altamente prevalente, distinta de la discapacidad y la comorbilidad, que incrementa la vulnerabilidad de los ancianos a eventos clínicamente relevantes, incluyendo deterioro funcional, caídas e institucionalización. Uno de los conceptos clave que subyace al síndrome de la fragilidad es la sarcopenia (pérdida de masa muscular, fuerza y función muscular asociada al envejecimiento). Uno de los principales factores precipitantes de la sarcopenia es la inactividad física que causa un deterioro global en la capacidad funcional y acaba desencadenando habitualmente fragilidad. En el diagnostico de la fragilidad se incluyen deterioro en parámetros físicos tales como una velocidad de la marcha enlentecida, cansancio, baja resistencia, baja actividad física y una fuerza de presión disminuida. Junto con la sarcopenia, la infiltración grasa del músculo esquelético, que se valora mediante la atenuación del tejido muscular, se asocia con un riesgo elevado de pérdida de movilidad en ancianos.

Con el envejecimiento, la potencia muscular se deteriora más precozmente que la fuerza muscular. En poblaciones ancianas, la potencia muscular se correlaciona de forma más significativa con la realización de pruebas funcionales que la fuerza muscular. Esta pérdida de potencia se asocia directamente con una reducción en la movilidad y en la capacidad de realizar actividades básicas o instrumentales de la vida diaria. Las mediciones de fuerza y de potencia deben acompañarse de otro tipo de parámetros conocidos como mediciones de capacidad funcional. Son muy útiles en la valoración de la fragilidad y frecuentemente se asocian con movilidad (p.e velocidad de la marcha, TUG, fuerza de presión). El conocimiento de las asociaciones entre la potencia, fuerza y masa muscular y la capacidad funcional puede mejorar las recomendaciones de prescripción de ejercicio en el anciano frágil.

El deterioro cognitivo leve (DCL) es un estado transicional entre el envejecimiento cognitivo normal y la demencia precoz. El deterioro cognitivo se ha relacionado de forma estrecha con la fragilidad ya que ambas entidades comparten mecanismos fisiopatológicos y consecuencias a corto y medio plazo (p.e.

hospitalizaciones, incidencia de caídas, discapacidad, institucionalización y muerte). Es bien conocido que los pacientes con demencia presentan algunos de los síntomas característicos del fenotipo de fragilidad tales como una velocidad de la marcha disminuida y una actividad física reducida. No obstante, la presencia de diferencias o similitudes en parámetros físicos en el anciano frágil con o sin deterioro cognitivo asociado no ha sido estudiada. Estas diferencias pueden ser particularmente evidentes mediante la realización de pruebas duales.

Dado que los parámetros físicos están relacionados con el síndrome de la fragilidad, la actividad física es uno de los componentes más importantes en la prevención y tratamiento de este síndrome. Los estudios previos sobre ejercicio físico en frágiles han demostrado que los programas de ejercicio multicomponente y especialmente el ejercicio de fuerza, constituyen las intervenciones más relevantes en retrasar la discapacidad y otros eventos adversos asociados al síndrome de la fragilidad. No obstante, sólo una pequeña parte de estos estudios se han centrado en los institucionalizados y en los "muy ancianos" y la mayoría fueron programas de corta duración. Los beneficios de un programa de ejercicio multicomponente (que incluya entrenamiento basado en la potencia, equilibrio y capacidad funcional) en ancianos frágiles nonagenarios e institucionalizados todavía permanece por aclarar completamente. Además, los datos de los efectos de estos programas en el tamaño muscular y en la infiltración grasa muscular son escasos.

La demencia es un síndrome que representa un problema público de salud en relación a su impacto en las AVD y en el deterioro de las funciones ocupaciones y sociales. Con la progresión de la demencia, los ancianos con deterioro cognitivo desarrollan fragilidad, discapacidad y frecuentemente institucionalización. Una de las principales consecuencias negativas de la demencia es el severo deterioro en la actividad física, que se puede atribuir a muchas causas y, entre ellas, al uso de restricciones físicas para prevenir caídas. Estas restricciones se asocian a consecuencias adversas desde el punto de vista fisiológico, físico y social tales como pérdida de libertad y autonomía, humillación, incontinencia, desmoralización, depresión, agresividad, exacerbamiento de la sarcopenia, pérdida de fuerza, deterioro en la capacidad de levantarse y caminar, y de forma global, deterioro funcional y de la calidad de vida. El síndrome de fragilidad, habitualmente presente en los ancianos con demencia, puede acelerar la trayectoria de deterioro en los ancianos con demencia. Las intervenciones con ejercicio físico (fuerza, caminar y ejercicios de equilibrio) que estan diseñadas para mejorar dominios físicos del síndrome de fragilidad pueden beneficiar también a los ancianos con demencia. De forma adicional, el ejercicio físico de fuerza y resistencia ha demostrado mejorar la función cognitiva de los pacientes con demencia. Sin embargo, hasta la fecha ningún estudio ha investigado los efectos de una intervención con ejercicio físico en ancianos frágiles con demencia después del uso a largo plazo de restricciones físicas. Además, se conoce poco los efectos regresivos del cese del entrenamiento en ancianos frágiles con demencia una vez el entrenamiento ha finalizado.

Para investigar los aspectos previamente mencionados, la presente Tesis Doctoral está compuesta de los siguientes estudios y respectivos objetivos. En el artículo de Revisión: buscar la literatura previa que demuestre que el ejercicio físico es una intervención eficaz en ancianos frágiles; Estudio I: Examinar las diferencias desde el punto de vista neuromuscular y funcional en ancianos frágiles "muy viejos" con y sin DCL; Estudio II: Investigar los efectos del entrenamiento multicomponente en la potencia muscular, masa y atenuación muscular tisular, riesgo de caídas y resultados funcionales en ancianos frágiles nonagenarios; Estudio III: examinar los efectos de un programa de ejercicio multicomponente en ancianos frágiles con demencia sobre la fuerza muscular, incidencia de caídas y parámetros funcionales después del uso continuado de restricciones físicas , seguido de 12 y 24 semanas de desentrenamiento.

En el artículo de revisión se mostraron las principales características del síndrome de fragilidad y se revisaron los test funcionales para el diagnóstico. Se analizaron las principales características del entrenamiento de fuerza y sus componentes en el anciano frágil. Se revisaron otros tipos de entrenamiento y el efecto del ejercicio físico en otros dominios de la fragilidad tales como las caídas, deterioro cognitivo y depresión. En el estudio I, 43 ancianos mujeres y varones (91.9+-4-1 años) se clasificaron en tres grupos: frágiles, frágiles+ DCL y el grupo no frágil. Se realizaron pruebas de fuerza en miembros superiores e inferiores. Las pruebas funcionales incluyeron Velocidad de la marcha 5 metros, TUG, pruebas duales, equilibrio y levantarse de la silla. Se utilizaron cuestionarios para registrar la incidencia de caídas. La masa muscular y la atenuación de la misma se midieron mediante tomografía computarizada. En el estudio II, 24 ancianos (91.9+-4.1) se aleatorizaron a control o intervención (ejercicio multicomponente). En ambos grupos se realizaron mediciones de fuerza, potencia, velocidad de marcha y TUG (con/sin pruebas duales) antes y después. El equilibrio se midió usando las pruebas FICSIT-4. Se midió la capacidad de levantarse de la silla y los datos de incidencia de caídas se recogieron usando cuestionarios. Previamente a las mediciones, se registró la situación funcional mediante la escala Barthel, Se midieron la masa muscular y la infiltración grasa mediante tomografía computerizada. En el Estudio III, se reclutaron 24 ancianos frágiles con demencia (88+-5.1 años). Se realizaron pruebas de fuerza, velocidad de marcha y TUG basales y con pruebas duales. Se midió el equilibrio y la capacidad de levantarse de la silla. La situación funcional de los participantes quedó registrada mediante el uso de la escala Barthel. El MMSE fue la prueba utilizada para la medición global de la cognición. Así mismo se examinaron la incidencia de caídas.

Los principales hallazgos del artículo de revisión fueron que los programas de ejercicio multicomponente, y especialmente el entrenamiento de fuerza, constituyen las intervenciones más relevantes para retrasar la discapacidad y otros eventos adversos asociados al síndrome de la fragilidad . Es más, estos programas constituyen intervenciones efectivas en otros dominios de la fragilidad tales como las caídas, deterioro cognitivo y depresión. En el estudio I, el principal hallazgo fue que los ancianos frágiles muy viejos con/sin DCL compartían similares resultados funcionales y neuromusculares. Además los resultados funcionales y la incidencia de caídas se asociaban con la masa muscular, fuerza y potencia. El principal resultado del estudio II fue la mejora significativa observada en el grupo intervención en el TUG basal y con pruebas duales, capacidad de levantarse de la silla, equilibrio y reducción en la incidencia de caídas. El grupo intervención se observó una mejoría de la potencia muscular y de la fuerza. Además, existieron mejorías en el área seccional muscular total y en las fibras musculares de alta densidad en el grupo intervención. En el estudio III, el principal resultado fue la ausencia de diferencias entre ambos grupos en la mayoría de parámetros funcionales después de 4 semanas de entrenamiento. No se objetivaron diferencias en la velocidad de la marcha 5 metros, TUG, realización de pruebas duales o en el número de levantadas desde la silla, mientras que sí que se objetivó una mejora significativa en las pruebas de equilibrio. Sin embargo, después de la segunda parte del entrenamiento, el grupo intervención necesito de forma significativa menos tiempo para la prueba del TUG y se observó mejoría en la mayoría de las mediciones de fuerza presión, flexión de cadera, extensión de rodilla y fuerza dinámica máxima . Así mismo se objetivó una reducción significativa en la incidencia de caídas. Después de 24 semanas de desentrenamiento se observó un deterioro marcado en la mayoría de los parámetros físicos.

Las conclusiones de la presente Tesis Doctoral fueron las siguientes: (I) Los programas de ejercicio multicomponente son estrategias eficaces para prevenir la discapacidad y otros dominios de la fragilidad tales como las caídas, deterioro cognitivo y depresión. Sin embargo, resulta necesario investigar cuales son los componentes óptimos de un programa de entrenamiento en un anciano frágil para desarrollar guías clínicas específicas de actividad física para esta población diana.(Artículo de revisión). (II) Los ancianos frágiles mas envejecidos presentan los mismos resultados funcionales y neuromusculares que aquellos en las mismas condiciones y que asocian DCL (Estudio I). (III) Los programas de ejercicio multicomponente deberían prescribirse de forma rutinaria en ancianos frágiles nonagenarios ya que mejoran significativamente la condición física global de este grupo poblacional (Estudio II). (IV) Una intervención de ejercicio multicomponente mejoró la fuerza muscular, el equilibrio y la marcha en ancianos frágiles con demencia, incluso después del uso continuado de restricciones físicas. Estos beneficios se perdieron después del cese del entrenamiento. (Estudio III)

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DLA	Daily living activities.
MCI	Mild Cognitive Impairment
TUG	Time up and go test
FICSIT-4	Frailty and Injuries: Cooperative Studies of Intervention Techniques
MMSE	Mini-Mental State Examination de Folstein
AVD	Actividades de la vida diaria
DCL	Deterioro cognitivo leve
1RM	One repetitions maximum
% 1RM	Porcentaje de fuerza dinámica máxima
%	Porcentual
COL	Colaboradores
ADL	Active daily living
ABVD	Actividades básicas de la vida diaria
AIVD	Actividades instrumentales de la vida diaria
SPPB	Short Performance Battery Test
SARM	Moduladores selectivos de los receptores androgénicos
RMN	Resonancia Magnética Nuclear
TAC	Tomografía Axial Computerizada
RM	Repetición máxima/Repetitions maximum
P.E	Por ejemplo
$V02_{max}$	Captación máxima de oxígeno
S	Entrenamiento exclusivo de fuerza
E	Entrenamiento exclusivo de resistencia
SE	Entrenamiento combinado (1 sesión/semana S + 1 sesión/semana E)
WL_{max}	Potencia máxima alcanzada durante un test progresivo hasta el agotamiento en cicloergómetro
AV	Aurículo- Ventricular
SD	Standard Deviation

CT	Computed Tomography
GVT	Gait velocity test
Verbal GVT	Gait velocity while performing a verbal task (dual task condition)
Counting GVT	Gait velocity while performing a arithmetic task (dual task condition)
M.S $_{-1}$	Average velocity
W	Mean power
CSA	Cross-sectional area
SAT	Subcutaneous adipose tissue
IMAT	Intermuscular adipose tissue
QF	Quadriceps Femoris
HU	Hounsfield units
HDM	High-density muscle
LDM	Low density muscle
MEC	Mini-examen cognoscitivo
BI	Barthel index
ADD	Adductor muscles
KF	Knee flexor muscles
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CDR	Clinical Dementia Rating

1. GENERAL INTRODUCTION

Frailty syndrome is an age-associated syndrome that is characterized by decreases in the functional reserve and resistance to stressors related to different physiological systems. This syndrome is strongly associated with sarcopenia and places older individuals at special risk for disability, hospitalization, and death induced by falls (Campbell and Buchner 1997; Walston and Fried 1999; Rockwood and Mitnitski 2007; Rodríguez Mañas *et al.* 2012). Along with sarcopenia, skeletal muscle fat infiltration, which is assessed through muscle tissue attenuation, is associated with an increased risk of mobility loss in older men and women (Visser *et al.* 2005). As a consequence of impaired muscle function, the diagnosis of frailty includes physical impairments, such as low gait speed, fatigue, and low grip strength (Fried *et al.* 2001; Bandeen-Roche *et al*. 2006; Garcia-Garcia *et al.* 2011; Cameron *et al.* 2013). Due to the physical domains that are related to frailty, physical activity is one of the most important components in the prevention and treatment of this syndrome. Indeed, the benefits of physical exercise in improving the functional capacity of frail older adults have been the focus of considerable recent research (Fiatarone *et al.* 1994; Hauer *et al.* 2001; Barnett *et al.* 2003; Lord *et al.* 2003; Serra-Rexach et al. 2011; Villareal et al. 2011; Clemson et al. 2012; Freiberger et *al.* 2012; Kim *et al.* 2012). In a recent systematic review that investigated the effectiveness of different exercise interventions on the incidence of falls, gait ability, balance, and strength, 70 % of the studies included showed a reduction in the incidence of falls, 54 % showed enhancements of gait ability, 80 %showed improvements in balance, and 70 % reported increases in muscle strength (Cadore *et al.* 2013). Although the effects of exercise interventions on functional outcomes in the frail elderly have been demonstrated, data on the effects of exercise programs on muscle size and muscle fat infiltration are scarce.

Of the above mentioned studies, only a small number focused on institutionalized very old frail patients (Fiatarone *et al.* 1994; Serra-Rexach *et al*. 2011). Fiatarone *et al.* (1994) showed that physically frail elderly subjects (72 to 98 years) showed improved habitual gait velocities, stair-climbing abilities, and strength after 10 weeks of resistance training. More recently, Serra-Rexach *et al.* (2011) reported that 8-week resistance and endurance training in 20 oldest old subjects (90–97 years of age) increased their leg press strength but no changes were observed in the time-up-and-go (TUG) or gait velocity. However, only the short-term resistance training program (8 weeks) used was not sufficient stimuli to improve all functional outcomes in the frail oldest old, suggesting that multicomponent exercise interventions composed of resistance, balance, and gait exercises may be necessary to improve the overall functional status of this very old population. Indeed, the benefits of a multicomponent exercise program that includes muscle power loading and balance and functional capacity stimulus in frail nonagenarians remain to be fully investigated.

Skeletal muscle power decreases before muscle strength with advancing age (Izquierdo *et al.* 1999; Reid and Fielding 2012) and is more strongly associated with functional test performance than muscle strength in elderly populations (Pereira *et al.* 2012). However, to the best of our knowledge, no study has investigated the effects of multicomponent exercise intervention, with a specific emphasis on muscle power output, balance, and walking enhancements, in the frail oldest old population

MCI is seen as a transitional state between normal cognitive aging and early dementia (Makizako *et al.* 2012; Lui- Ambrose *et al.* 2010). Recent studies have shown that older adults with MCI have a higher prevalence of gait impairments than cognitively normal older adults and that having MCI predicts the later development of dementia (Montero-Odasso *et al.* 2012). Cognitive impairment has been closely related to frailty because both diseases share some pathophysiological mechanisms and short-term and mid-term consequences (e.g., hospitalization, incidence of falls, disability, institutionalization, and death) (Garcia-Garcia *et al.* 2011). In addition, muscular and central nervous systems share common pathogenic pathways in the evolution of disability, probably underlying the negative association between muscle strength and cognitive impairment (Zwijsen *et al.* 2011; Uemura *et al.* 2013). It is well known that people with dementia exhibit some of the symptoms of the frailty phenotype such as a low gait velocity and a low level of physical activity (Garcia-Garcia *et al.* 2011) but the presence of similarities of differences in the physical outcomes in the frail elderly with or without cognitive impairment has not been studied. These differences could be particularly evident during the dual-task gait paradigm.

Gait impairment is one of the most consistent predictors of falls and is a prevalent feature among older adults with cognitive impairment and frailty syndrome

(Fried *et al.* 2001). Traditional gait assessment is not sensitive enough to detect subtle gait impairments. A sensitive method for detecting these early interactions is to measure the effect that a cognitive load (e.g. simultaneous talking or counting while walking) has on gait. Because one study demonstrated that the inability to maintain a conversation while walking ("stops walking while talking") is a marker for future falls in older adults (Lundin-Olsson *et al.* 1997) walking while performing a secondary task (the dual-task paradigm) has become the classic way to assess the interaction between cognition and gait (Montero-Odasso *et al.* 2012; Makizako *et al.* 2012; Doi *et al.* 2011). Dual-task tests reflect executive function, which is an essential cognitive resource for normal walking. However, little attention has been given to the relationship between dual tasks and frailty or to the ability of these tasks to detect subtle differences in gait patterns between frail patients with and without MCI.

Dementia is a syndrome that represents a major public health problem because it impacts the capacity for active daily living (ADL) and impairs social and occupational functions (Heyn *et al.* 2004). With the progression of dementia, elderly individuals with cognitive disorders generally become frail and institutionalized patients (Heyn *et al.* 2004; Singh *et al.* 2002). One of the major negative consequences of dementia is the severe decline in physical activity, which can be attributed to several causes, including the use of physical restraints to prevent falls (Gulpers *et al.* 2010). Physical restraints, which are commonly used in elderly individuals who require long-term nursing care (Zwijsen *et al.* 2011) may be defined as any limitation of an individual's freedom of movement (Hamers *et al.* 2005) and include restraints worn by the person (belt, chest and arm/leg) and those attached to beds (full-enclosure bed rails) or chairs (locked table) (Gulpers *et al.* 2010). The restraints are associated with adverse social, physical and psychological outcomes, such as loss of freedom and autonomy, humiliation, incontinence, demoralization, depression, aggression, exacerbated sarcopenia, loss of strength, impaired ability to stand and walk and overall decreased functional status and quality of life (Gulpers *et al.* 2010; Zwijsen *et al.* 2011).

Dementia and frailty may coexist in elderly persons because both diseases share several pathophysiological mechanisms and phenotypes and are different entities in the same disease spectrum (Garcia-Garcia *et al.* 2011). Long term physical restraint of elderly individuals as a consequence of dementia and institutionalization may accelerate sarcopenia (Gulpers *et al.* 2010) which, in addition to strength and muscle power loss, results in an accelerated decline in aspects of overall function including gait ability in addition to other physical hallmarks present in frail elderly patients (Rockwood *et al.* 2007; Rodriguez-Mañas *et al.* 2012; Bergman *et al.* 2007; Morie *et al.* 2010). The frailty syndrome may accelerate the trajectory of decline in patients with dementia because individual components of frailty, such as impaired grip strength, slow gait, low level of physical activity and body weight loss, have been shown to predict the development of dementia and are associated with the incidence of mild cognitive impairment (MCI) (Watson *et al.* 2010; Yaffe *et al.* 2009; Boyle *et al.* 2010; Garcia-Garcia *et al.* 2011).

Exercise intervention (e.g., resistance, walking and balance training), which is designed to improve the physical domains of frailty, may also benefit elderly patients with dementia (Hauer *et al.* 2012). Additionally, physical exercise, such as endurance and resistance training, has been shown to improve cognitive function in subjects with MCI and dementia (Heyn *et al.* 2004; Hauer *et al.* 2012; Liu-Ambrose *et al.* 2010). However, to the best of our knowledge, no study has investigated the effects of exercise intervention in frail subjects with dementia after long-term physical restraint. Dual-task walking, such as "walking when talking", has become an interesting method to assess the interaction among cognition, gait and falls because results in dual-task walking tests are associated with the incidence and risk of falls (Montero-Odasso *et al.* 2012; Lundin-Olsson *et al.* 1997) However, the effects of an exercise program on dual-task performance have not been investigated in frail elderly patients with dementia.

Physically frail patients with dementia often experience interruptions in training sessions because of illness, injury or other factors that may result in a reduction or cessation of their normal physical activity. Reports have shown that cessation of training results in a loss of strength and that the magnitude of this reduction may depend on the length of the detraining period (Izquierdo *et al.* 2007; Pereira *et al.* 2012) together with the subject's pretraining physical level. However, little is known about the regressive effects of training cessation in frail elderly patients with dementia once the training intervention has ended (Henwood *et al.* 2008). Therefore, the extent to which the residual effects of power or strength training promote physical independence after a period of interruption needs to be elucidated.

2. REVIEW OF THE LITERATURE

Ejercicio físico como intervención eficaz en el anciano frágil

Physical exercise as an efficient intervention in frail elderly persons

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An. Sist. Sanit. Navar. 2012, Vol. 35, Nº 1, enero-abril

Resumen

El síndrome de la fragilidad define a los ancianos vulnerables que tienen un riesgo elevado de sufrir eventos adversos. Su fisiopatología y etiopatogenia es compleja, pero actualmente disponemos de medidas sencillas de capacidad funcional para su evaluación. La inactividad física, que frecuentemente asocia el envejecimiento, es uno de los factores fundamentales que contribuye a la aparición de sarcopenia, aspecto central de la fragilidad. Los programas de ejercicio físico multicomponente y, particularmente el entrenamiento de la fuerza, constituyen las intervenciones más eficaces para retrasar la discapacidad y otros eventos adversos. Así mismo, han demostrado su utilidad en otros dominios frecuentemente asociados a este síndrome como las caídas, el deterioro cognitivo y la depresión. Sin embargo, es necesario investigar cuáles son los componentes óptimos de un programa de fuerza en el frágil, así como la óptima relación dosis-respuesta que permita desarrollar guías clínicas específicas de actividad física para este grupo poblacional.

Palabras clave. Entrenamiento de fuerza. Capacidad aeróbica. Fragilidad. Envejecimiento.

Abstract

Frailty is a state of vulnerability that involves an increased risk of adverse events in older adults. It is a condition with a complex etiology and pathophysiology. At present, there are functional tools for its assessment that are simple and reliable. Physical inactivity is a major risk factor for sarcopenia, a core aspect of frailty. Currently, mulicomponent exercise programs, and especially resistance exercise, are the most relevant interventions to slow down disability and other adverse outcomes. Moreover, these programs are valuable interventions in other frailty domains such as falls, cognitive decline and depression. However, in frail aged patients it is necessary to explore optimal resistance training components and develop specific clinical guides of physical activity for this target population.

Key words. Strength training. Frailty. Aerobic capacity.Aging.

FRAGILIDAD. Concepto, valoración e indicadores funcionales

El perfil demográfico de España ha experimentado un cambio espectacular a lo largo del pasado siglo; la población general española se duplicó, la de mayores de 65años se multiplicó por 7 y la de octogenarios por 13. Así, hemos pasado de tener un 11,24% de personas mayores de 65 años en1981 al 16,86% en el año 2000 (Cassel 2002; Morley 2004). En dicho año, había 6.842.143 de personas mayores de 65 años y 1.545.994 mayores de 80 censadas en España. Las previsiones para la primera mitad del siglo no sólo no modifican la tendencia, sino que la confirman, situando el porcentaje de mayores de 65 años en un 20% en el año 2021 (Morley 2004). Esto nos convertiría en el país con mayor porcentaje de personas mayores a nivel mundial en la primera mitad del siglo XXI. Estos datos justifican la necesidad de examinar el impacto del envejecimiento y el ejercicio físico sobre la salud, con el fin de prevenir sus consecuencias indeseables, mejorar el bienestar de los ancianos y facilitar su adaptación a la sociedad en que viven.

El interés sobre el envejecimiento ha crecido exponencialmente en las últimas décadas. Alguno de sus aspectos, como la discapacidad y la fragilidad, se han convertido en centro de atención de la investigación básica, clínica y poblacional. Como consecuencia de la mayor longevidad poblacional hemos asistido a un cambio en los patrones de enfermar en lo que se conoce cómo transición epidemiológica. Así la enfermedad aguda, de curso exógeno y transmisible se ha reemplazado por la edad-dependiente, origen endógeno, curso crónico y generalmente no transmisible (De la Fuente 2001). En la mayoría de las ocasiones, conforme un individuo envejece (envejecimiento habitual o “usual aging”) se produce un deterioro progresivo de la adaptabilidad al deteriorarse tanto la reserva funcional en múltiples niveles celulares como el control del medio interno (homeostasis). Dicha pérdida condiciona una mayor susceptibilidad a la agresión externa, al disminuir los mecanismos de respuesta y su eficacia para conservar el medio interno. Esta vulnerabilidad es el substrato fisiopatológico fundamental de la fragilidad (De la Fuente 2001).

Los datos epidemiológicos del *Cardiovascular Health Study* demuestran que el síndrome tiene un alto impacto en la población, con una prevalencia de sujetos frágiles del 7% entre los mayores de 65 años y de pre-frágiles del 47% (Fried *et al.* 2001). Los estudios españoles corroboran los datos americanos. Así, en el Estudio Toledo para un Envejecimiento Saludable (ETES) (García Garcia *et al.* 2011) arroja una prevalencia de fragilidad del 8,4% (mayores de 64 años) y muestra una clara relación con la edad. En el estudio FRADEA de Albacete (Abizanda *et al.* 2011) la prevalencia alcanza el 16,9% (mayores de 69 años).

Actualmente no existe un consenso sobre cuáles son los parámetros o dominios que mejor definen el síndrome de la fragilidad. A pesar de estas imprecisiones en cuanto a definición, biología, causas y diagnóstico de la fragilidad (Rockwood *et al.* 2007) existen varias certezas intuitivas, como son:

– Asociación con un riesgo incrementado de resultados adversos (caídas, anorexia-pérdida de peso, delirium, hospitalización, declive funcional, deterioro cognitivo, mortalidad, ingreso en residencia).

– Afectación de múltiples órganos como sustrato y consecuente aparición de vulnerabilidad, así como cambios que se producen en el tiempo (Rockwood *et al.* 2007).

Dos modelos han demostrado validez en el concepto y en la predicción de eventos adversos:

– Fenotipo físico de fragilidad: propuesto por Fried *et al.* en el año 2001 incluye los siguientes dominios: pérdida de peso no intencionada (>4,5kg/año) debilidad (medida a través de la fuerza de prensión), cansancio, baja resistencia, lentitud (medida mediante velocidad de la marcha) y bajo grado de actividad física. Los sujetos con uno o 2 criterios se consideran pre-frágiles y aquellos con 3o más criterios se consideran frágiles.

– Modelo de múltiples dominios (Rockwood *et al.* 2007) postulado por diferentes autores como Rockwood o Mitniski, implica que la presencia de diversas afecciones (enfermedades, síndromes geriátricos, discapacidades y factores psicosociales) asociadas al envejecimiento se agrupan de manera aditiva para originar vulnerabilidad.

Sea cual sea el modelo y los dominios afectos en lo que sí existe consenso es en la existencia de una mayor vulnerabilidad o estado de pre-discapacidad y la predisposición a eventos adversos (discapacidad, institucionalización, muerte, caídas, fracturas y hospitalizaciones) (Abizanda Soler *et al.* 2010) derivada de una pérdida de homeostasis, debido a un declive en múltiples sistemas corporales (neuromuscular, metabólico-inflamatorio, neuroendocrino, vascular) (Bergman *et al.* 2007). La consecuencia del deterioro en estos sistemas es la disminución de la reserva funcional y la aparición de sarcopenia −deterioro de la función muscular asociado al envejecimiento−, aspecto central de la fragilidad. La vía final común de este ciclo suele desembocaren la aparición de discapacidad y dependencia (Fried *et al.* 2001) (Fig. 1).

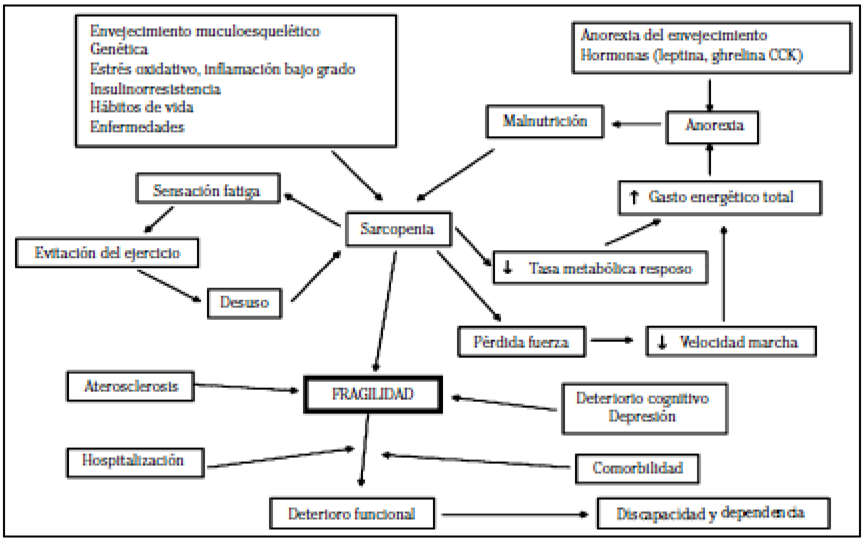

Figura 1. Ciclo de la Fragilidad (Abizanda *et al.*, 2010)

La pérdida de masa y cualidades musculares, especialmente la potencia muscular, que acontece en el envejecimiento y en la fragilidad está directamente relacionada con una reducción en la movilidad y en la capacidad de realizar las denominadas actividades básicas o instrumentales de la vida diaria (ABVD o AIVD) (Rantanen *et al.* 1998). El desempeño de estas actividades está relacionada con múltiples variables (p.e. comorbilidad, regulación hormonal y función cognitiva). No obstante, las relaciones entre parámetros de fuerza y capacidad en AVD no son lineales (Jette *et al.* 1997), por lo que para tratar de explicarlas bases etiopatogénicas de la fragilidad, las medidas de función muscular se deben acompañar de otro tipo de mediciones. Estas medidas se denominan “medidas de rendimiento o capacidad funcional” y su utilidad a la hora de cuantificar la limitación funcional hace que se hayan utilizado en numerosos estudios clínicos y epidemiológicos, constituyendo un instrumento fundamental en la valoración de la fragilidad y en la predicción de eventos adversos. Dentro de estas mediciones ocupan un lugar de privilegio aquellas relacionadas con la movilidad. Entre ellas podemos destacarlas siguientes:

Velocidad de la marcha. Es el tiempo empleado en recorrer una distancia predeterminada, habitualmente entre 4 y 8 metros. Muchos autores consideran que puede ser una buena herramienta para detectar fragilidad (Abellan Van Kan *et al.* 2010), eventos adversos (Montero-Odasso *et al.* 2005) y supervivencia (Studenski *et al.* 2011). Destaca por su utilidad, simplicidad y reproducibilidad en la práctica clínica diaria. Una velocidad de la marcha superior a 1,1 m/s puede ser considerada como normal en ancianos comunitarios sin discapacidad, mientras que cuando es inferior a 0,8m/s detecta problemas en la movilidad y predice caídas, incluso con mayor precisión que otras pruebas funcionales ((Montero-Odasso *et al.* 2005). Una velocidad menor 0,6 m/s predice eventos adversos. Un punto de corte menor de 1 m/s se considera un buen marcador de fragilidad (Cesari *et al.* 2005).

Time Up and Go. Desarrollado por Podsiadlo *et al.* en 1991, comprende el tiempo invertido en levantarse de la silla sin utilizar los brazos, caminar durante 3 metros, darse la vuelta y volver a la silla y sentarse. Una puntuación inferior a 10 segundos es normal; entre 10 y 20 segundos es marcador de fragilidad y cuando es mayor de 20 segundos se considera que el anciano tiene un elevado riesgo de caídas (Abizanda Soler *et al.* 2010).

SPPB (Short Performance Battery Test). Es una herramienta eficaz para la valoración de la función física en el anciano. Combina mediciones de equilibrio (bipedestación, tándem y semitándem), marcha (velocidad de la marcha 4 m), fuerza y resistencia (levantarse de la silla). Su puntuación se correlaciona de forma significativa con institucionalización y mortalidad (Guralnik *et al.* 1994).

Prueba de estación unipodal. Se ha demostrado que es una herramienta útil a la hora de predecir el riesgo de caída en población anciana. Una puntuación inferior a 30 segundos se asocia con historia previa de caídas mientras que un valor superior a 30 segundos se asocia con un bajo riesgo de caída (Hurvitz *et al.* 2000). Recientemente, se ha observado que esta prueba se asocia con riesgo de fragilidad (Martinez-Ramirez *et al.* 2011).

Fuerza de prensión en mano dominante. La pérdida de la fuerza de prensión se asocia con el envejecimiento, pero independientemente de esta relación, se ha demostrado que es un potente predictor de discapacidad, morbilidad y mortalidad y por sí solo es buen marcador de fragilidad (Syddali *et al.* 2003).

El principal objetivo en la fragilidad, una vez se ha realizado una adecuada detección de la misma, es la intervención precoz con el objetivo de prevenir el deterioro funcional y la dependencia o al menos poder ralentizar o retrasar su aparición. En un síndrome donde la etiopatogenia es compleja e intervienen múltiples vías, tiene sentido que las intervenciones sean multifactoriales. En los últimos años se han desarrollado avances en intervenciones nutricionales (suplementos proteínicos, vitamina D), farmacológicas (miméticos dela ghrelina, moduladores selectivos de los receptores androgénicos-SARM, antimiostáticos, antioxidantes y creatina), aunque la intervención que mejor resultado ha conseguido es el ejercicio físico (Abizanda *et al.* 2010).

Envejecimiento y sistema neuromuscular

Con el envejecimiento, la capacidad funcional del sistema neuromuscular, cardiovascular y respiratorio comienza a disminuir de forma progresiva lo que conlleva un riesgo aumentado de fragilidad. Diversos estudios (Hakkinen *et al.* 1998; Izquierdo *et al.* 1999; Izquierdo *et al.* 1999) han observado que las personas de 75 años presentan, con respecto a los jóvenes de 20 años, una disminución de la resistencia aeróbica (45%), fuerza de prensión (40%), fuerza de las piernas(70%), movilidad articular (50%) y de la coordinación neuromuscular (90%). La sarcopenia es uno de los principales factores que influyen en la disminución de la capacidad de mantenerse independiente en la comunidad y en la génesis de la discapacidad (Cruz-Jentoft *et al.* 2010). La fuerza máxima y explosiva es necesaria para poder realizar muchas tareas de la vida diaria como subir escaleras, levantarse de una silla o pasear. Por otro lado, también es conocido que la reducción de la capacidad del sistema neuromuscular para generar fuerza que aparece con el envejecimiento también favorece el riesgo de caídas, típicas de este grupo de población.

Además del envejecimiento “per se” uno de los factores que mejor explican la reducción de fuerza y la masa muscular asociada al envejecimiento, es la drástica reducción que se observa con el paso de los años en la cantidad y calidad de actividad física diaria. La estimación media de pérdida de masa muscular a partir de los 60 años es de 2 kg en varones y 1 kg en mujeres (Janssen *et al.* 2000), pero sólo 10 días de reposo en cama en un anciano puede resultar en un pérdida de 1,5 kg de masa magra (fundamentalmente en miembros inferiores) y una disminución del 15% de la fuerza de extensión de la rodilla (Kortebein *et al.* 2007). La inmovilización además induce resistencia anabólica (Glover *et al.* 2008), disfunción mitocondrial y apoptosis (Marzetti *et al.* 2006). El resultado de todo este proceso, como si se tratase de un círculo vicioso, origina que en la medida en que disminuye la práctica de actividad física diaria, disminuye la fuerza y la masa muscular lo que a su vez genera mayor sarcopenia (Fig. 2). La interrupción de este ciclo es de vital importancia para el mantenimiento de la funcionalidad de los ancianos.

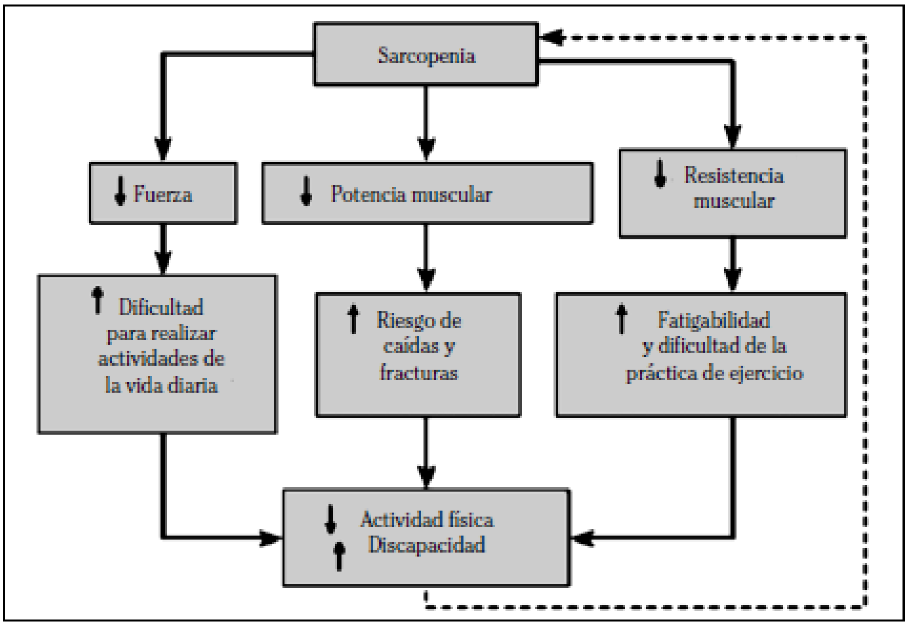

Figura 2. Modelo que explica las consecuencias funcionales de los cambios relacionados con la edad en la sarcopenia (pérdida de masa y función muscular) y el ciclo por el que se explica cómo la reducción de la actividad física acentúa el proceso de alteración. (Modificado de Hunter *et al.* 2004)

En las últimas décadas se ha propugnado que el entrenamiento de fuerza en personas mayores podría prevenir o retardar la pérdida de fuerza. Diversos estudios han mostrado que la realización de un entrenamiento sistemático de la fuerza máxima se acompaña de incrementos significativos en la producción de fuerza, no sólo en personas jóvenes, sino también en las mayores (Hakkinen *et al.* 1998; Izquierdo *et al.* 2001). Los incrementos iniciales de la fuerza pueden llegar a ser de hasta un10-30% (o incluso más) durante las primeras semanas ó 1-2 meses de entrenamiento, tanto en personas de mediana edad como en las de edad avanzada, en ambos sexos. En los siguientes apartados se examinarán los efectos de los distintos programas de ejercicio físico en el anciano frágil.

Entrenamiento de fuerza en el anciano frágil

Los programas de entrenamiento de fuerza en mayores probablemente constituyen por sí mismos la medida preventiva más eficaz para retrasar la aparición de sarcopenia y/o fragilidad (Rolland *et al.* 2011). Varios estudios y revisiones sistemáticas han demostrado que incluso en los ancianos más viejos y frágiles el entrenamiento de fuerza aumenta la masa muscular, la potencia y la fuerza muscular (Latham *et al.* 2004; Liu *et al.* 2009; Hasten *et al.* 2000) además de mejorar parámetros objetivos del síndrome de fragilidad, tales como la velocidad de la marcha y el tiempo de levantarse de una silla (Liu *et al.* 2009). Aunque inicialmente sus resultados sobre la mejoría de la función no eran claros, la reciente revisión sistemática realizada por Liu y Lathman (2009) ha demostrado que es una intervención eficaz para mejorar la función física en ancianos y retrasar por lo tanto la discapacidad, que es el principal evento adverso de la fragilidad.

La realización de un entrenamiento sistemático de fuerza máxima en mayores se acompaña de incrementos significativos en la producción de fuerza siempre y cuando la intensidad y duración del periodo de entrenamiento sean suficientes (Hakkinen *et al* 1998; Izquierdo *et al.* 2001; Pederesen *et al.* 2006). Los incrementos de fuerza inducidos por el entrenamiento se asocian en las primeras semanas de entrenamiento, principalmente a una adaptación en el sistema nervioso, ya sea por un aumento en la activación de la musculatura agonista o bien por cambios en los patrones de activación de la musculatura antagonista. Sin embargo, a partir de la semana 6-7 la hipertrofia muscular es un hecho evidente, aunque los cambios en los tipos de proteínas, tipos de fibras y síntesis de proteínas ocurran mucho antes.

El músculo esquelético tiene la capacidad de hipertrofiarse después de participar en un programa de entrenamiento de fuerza. La hipertrofia muscular es resultado de la acumulación de proteínas, debido a un aumento en la síntesis, reducción en la degradación o ambos. A pesar de que en los ancianos el incremento de la fuerza muscular con el entrenamiento es debido principalmente a mejoras en los patrones de activación neural, se ha demostrado que la hipertrofia muscular también contribuye a la mejora de la fuerza. Esto se ha reflejado en estudios en los que se han utilizado técnicas sensibles como la determinación del área de las fibras musculares mediante la realización de biopsias musculares, o la determinación del área de la sección transversal muscular mediante el uso de RMN o TAC (Frontera *et al.* 1988; Treuth *et al.* 1994). Algunos estudios experimentales han mostrado en grupos de personas de edad avanzada, diferencias significativas en el área de la sección transversal muscular del grupo muscular cuádriceps femoral medida antes y después de sólo 2-3 meses de un entrenamiento de fuerza (Frontera *et al.* 1988; Hakkinen *et al.* 1995). Sin embargo, los efectos del entrenamiento sobre el área de la sección transversal muscular se tienen que interpretar con cautela debido a que la hipertrofia muscular inducida por el entrenamiento de fuerza puede no ser un proceso uniforme a lo largo de todo el paquete muscular (Hakkinen *et al.* 2001). Así, en un estudio realizado por Häkkinen *et al.* en mujeres de avanzada edad se observó que los cambios inducidos tras 21 semanas de entrenamiento de fuerza en el área de sección transversal determinada por resonancia magnética nuclear, no eran uniformes a lo largo de grupo muscular cuádriceps femoral, de tal forma que los aumentos fueron superiores en las regiones con más sección transversal, en las porciones proximales del vasto lateral y en las porciones distales del vasto medial. Sin embargo, estos hallazgos no se observaron en los músculos vastos intermedios y rectos femorales. Por otro lado, la influencia que tiene la proporción de fibras rápidas y lentas sobre los incrementos en la fuerza muscular y área de sección transversal, en respuesta al entrenamiento de fuerza en ancianos no está clara. Así, en un grupo de personas jóvenes y mayores, los sujetos con una proporción mayor de fibras musculares rápidas mostraron mayores incrementos en el área de sección transversal de los músculos entrenados que aquellos sujetos que tenían una menor proporción de fibras rápidas (Hakkinen *et al.* 2000). Esto podría ser de gran importancia si la pérdida de fibras musculares que se produce con el envejecimiento realmente afectara en mayor medida a las fibras musculares de contracción rápida, tal y como han sugerido algunos estudios. No obstante, diversos estudios también han observado aumentos en el tamaño de las fibras musculares tipo I y tipo II, acompañados de una transformación desde las fibras tipo IIx hacia las de tipo IIax y IIa (Hakkinen et al. 1998). Sin embargo, la magnitud de la hipertrofia provocada por el entrenamiento no se correlaciona necesariamente con los incrementos observados en la fuerza máxima durante periodos de pocas semanas (Moritani *et al.* 1980; Frontera *et al.* 1980). Esto puede explicarse por cambios a nivel del sistema nervioso y por pequeñas modificaciones en las propiedades contráctiles de las fibras con el entrenamiento.

Las adaptaciones producidas por un programa de entrenamiento de fuerza en mayores serán diferentes entre las personas y vendrán determinadas por su nivel de entrenamiento previo, situación funcional y comorbilidad asociada (Pedersen *et al.* 2006). Un anciano vigoroso con funcionalidad conservada, sin comorbilidad y con un nivel de actividad física previa elevado, necesitará un tipo de entrenamiento más exigente que aquel que sea frágil y presente patologías asociadas que afecten a su función, que deberá comenzar el programa con un estímulo menor. En la actualidad, las recomendaciones realizadas por algunas instituciones y autores (Physical Activity Guidelines Advisory Committee Report, 2008) suelen ser demasiado intensas y fatigantes y no están específicamente diseñadas para el anciano frágil. Pueden inducir un aumento del riesgo de lesión, abandono y sobre-entrenamiento, además de no favorecer en mayor medida el desarrollo de la fuerza y masa muscular que los efectos que pudieran surtir de utilizar intensidades inferiores. En los siguientes apartados se hará una revisión de los principales trabajos de investigación que abordan estas controversias y se presentarán algunas recomendaciones para la prescripción del entrenamiento de fuerza en ancianos frágiles.

Componentes del entrenamiento para el desarrollo de la fuerza

Las personas mayores retienen la capacidad de mejorar su fuerza muscular después de participar en un programa de entrenamiento sistemático de fuerza máxima siempre y cuando la intensidad y duración del periodo de entrenamiento sean suficientes (Perdersen *et al.* 2006). Estos programas deberán seguir los mismos principios básicos de entrenamiento que los diseñados para jóvenes o deportistas: 1) principio de la sobrecarga, 2) de la progresión, 3) de la especificidad y la individualidad del entrenamiento, y 4) del desentrenamiento o reversibilidad (American College of Sports Medicine Position Stand 1998). Así, este tipo de programa de entrenamiento deberá producir un estímulo lo suficientemente intenso, por encima del que suponen las actividades regulares de la vida diaria, como para producir la respuesta de adaptación deseada (principio de sobrecarga), pero sin llegar a producir agotamiento o esfuerzo indebido. Una vez que el organismo se adapte a este estímulo será necesario que se modifique y/o incremente, para que se continúe progresando (principio de la progresión). Si las cargas de entrenamiento no se incrementan progresivamente (entrenamiento de fuerza progresivo), los músculos se adaptarán al nivel de fuerza solicitado y se mantendrán los mismos niveles de fuerza hasta que no se someta al sistema neuromuscular a un estímulo mayor. Cuando una persona deja de entrenar, se producirá la regresión de las adaptaciones conseguidas. Además, el entrenamiento de fuerza deberá ser específico para los grupos musculares más utilizados y con transferencia directa (principio de especificidad) a actividades de la vida diaria como, por ejemplo, sostener una bolsa de la compra o subir escaleras.

La efectividad y resultado de un entrenamiento para el desarrollo de la fuerza depende de la aplicación de una carga adecuada, es decir, de factores como la intensidad, volumen de entrenamiento (series por repeticiones), frecuencia y tipología de los ejercicios recomendados (isocinético/resistencia variable/isoinercial), periodos de recuperación entre las series y la frecuencia de entrenamiento. Diferentes combinaciones de las variables que componen el entrenamiento, como por ejemplo el número de repeticiones por serie, número de series y descanso entre series, originan diferentes respuestas fisiológicas. De manera general, todos los programas de entrenamiento inducen ciertas mejoras de la fuerza máxima, hipertrofia o potencia muscular. Sin embargo, determinadas combinaciones tendrán un especial énfasis de adaptación en unas o en otras manifestaciones de la fuerza. Por ejemplo, en el trabajo realizado por Kraemer *et al.* (1990) se observó que 3 series de 10 repeticiones máximas (10RM) con 1 minuto de descanso entre series aumentaba significativamente la concentración de lactato y la hormona del crecimiento en comparación con la realización de 3 series a una intensidad de 5RM con 3 minutos de descanso. Por tanto, según estos estudios parece evidente que si el objetivo del entrenamiento es desarrollar la capacidad de tolerar la acidosis láctica y aumentar la hipertrofia muscular, este tipo de diseño de entrenamiento será el más efectivo. En los siguientes apartados se especificarán estas características para el desarrollo de la fuerza máxima con la influencia de tipo neural o hipertrófica y el desarrollo de la potencia muscular.

Intensidad

La intensidad de un estímulo es el grado de esfuerzo que exige un ejercicio, en el entrenamiento con cargas. Viene representado por el peso que se utiliza en términos absolutos o relativos, así como por el número máximo de repeticiones que se pueden realizar con un determinado peso (Physical Activity Guidelines Advisory Committee Report 2008; American College of Sport Medicine Position Stand 1998; Izquierdo *et al.* 2004). En función del número de repeticiones que se pueden realizar con una carga determinada hasta la fatiga se producen diferentes efectos sobre la fuerza. Clásicamente se ha comentado que el desarrollo de la fuerza máxima se consigue más eficazmente con cargas elevadas y pocas repeticiones máximas (RM) (desde 4RM-10RM), mientras que si se reduce la resistencia y se aumenta el número de repeticiones (12RM-20RM) se favorecerá el desarrollo de la resistencia muscular (Moritani *et al.* 1980; American College of Sport Medicine Position Stand 1998). A efectos prácticos, el porcentaje de la fuerza dinámica máxima (% de 1RM) correspondiente al peso con el que se podrían efectuar un máximo de 8 a 12 repeticiones, se encuentra aproximadamente, entre el 70-80%. La zona de 15 a 20 repeticiones corresponde a un 50-60% de 1RM. Para población anciana las recomendaciones del Colegio Americano de Medicina del Deporte en cuanto a la intensidad son inferiores, de 10-15RM (65-75%) aunque no existen recomendaciones específicas para los frágiles (American College of Sport Medicine Position Stand 1998). Sin embargo, cada vez parece más evidente que, la realización de repeticiones hasta el fallo con estas intensidades pueden suponer un excesivo e innecesario esfuerzo, además de ser perjudiciales para la salud y el rendimiento, no sólo para estos grupos de poblaciones especiales (p.e. envejecimiento, obesidad, diabetes), sino también para la mayoría de los deportistas. Por otro lado, existe poca evidencia que muestre el efecto superior de estas intensidades sobre otras más inferiores (p.e. 20RM-30RM) en personas previamente no entrenadas o en deportes con necesidades medias de fuerza (Izquierdo *et al.* 2004; Izquierdo-Gabarren *et al.* 2010; Izquierdo *et al.* 2006). Una revisión reciente (Steib *et al.* 2010) que analiza cuáles deben ser las intensidades del entrenamiento de fuerza en población anciana (no se especifica si frágil), concluye que intensidades elevadas son superiores a las bajas en términos de mejoría de fuerza máxima pero no necesariamente en términos de ganancias funcionales.

Potencia Muscular

La potencia es el producto de la fuerza y de la velocidad, es decir la situación en la que se obtiene el máximo rendimiento muscular. Cuando la resistencia a vencer es ligera, la fuerza máxima tiene poca importancia en la producción de potencia pero su influencia aumenta a medida que se incrementa la resistencia. Durante el envejecimiento, la potencia se deteriora más rápida y precozmente que la fuerza (Hakkinen *et al.* 1998; Izquierdo *et al.* 1999). Es más, la potencia muscular tiene una relación más significativa con la capacidad funcional del anciano que la fuerza (Tschopp *et al.* 2011). Además del efecto del envejecimiento sobre la potencia muscular, existen cambios a nivel del sistema nervioso, como el deterioro en la activación neuromuscular voluntaria, que pueden contribuir a reducir la potencia (Clark *et al.* 2010). En los ancianos (incluso en los más viejos) se puede mejorar la potencia mediante el entrenamiento al 60% de 1RM y con la máxima velocidad a esta resistencia (p.e. tan rápido como sea posible) que estará entre el 33-60% de la velocidad máxima sin resistencia (Clark *et al.* 2010; Kawamori *et al.* 2004).

Estudios realizados en la década pasada han demostrado en el anciano que el entrenamiento combinado de fuerza máxima y potencia muscular con duraciones desde 10 hasta 48 semanas, permite mejorar significativamente la fuerza máxima dinámica (Hakkinen *et al.* 1998). Estudios en ancianos jóvenes no frágiles (media de 64 años) comparativamente con adultos de mediana edad, han objetivado similares mejorías en términos de potencia muscular tras cuatro meses de entrenamiento, lo que supone recuperar hasta 20 años de edad funcional en términos de potencia muscular (Izquierdo *et al.* 2001).

En relación a lo expuesto anteriormente, podría plantearse que el entrenamiento basado en la potencia muscular (altas velocidades) podría ser más beneficioso en términos de mejorías funcionales que los programas de resistencia (bajas velocidades). Un metanálisis reciente (Tschopp *et al.* 2011) que revisa 11 estudios y analiza esta hipótesis, llega a la conclusión que parece haber beneficios funcionales en entrenamientos a altas velocidades, pero no resultan clínicamente relevantes. La totalidad de los estudios se realizaron en ancianos no frágiles, por lo que los autores recomiendan su prescripción en ancianos "sanos" ya que además, no se pudieron sacar conclusiones sobre su seguridad. Por lo tanto, en el anciano frágil, lo parece más razonable recomendar un programa de entrenamiento de fuerza con velocidades bajas y moderadas.

Volumen y frecuencia de entrenamiento

El volumen de entrenamiento es una medida de la cantidad total de ejercicio efectuado. Se expresa en función del número de repeticiones, kilogramos totales levantados, o duración de la sesión o período de entrenamiento. Clásicamente, los programas de entrenamiento para el desarrollo de la fuerza recomiendan realizar tres series de 6-12 repeticiones, durante 3 días a la semana. Una de las controversias en el entrenamiento de fuerza se deriva del volumen de entrenamiento utilizado. Los estudios experimentales parecen indicar que no se puede aceptar que cuanto más volumen se pueda realizar mejor será el resultado. Esta controversia se ha centrado en el debate relacionado con la utilización de una o más series por ejercicio. Existen propuestas que indican que los programas que utilizan una serie por ejercicio obtienen incrementos de parecida magnitud que aquellos que utilizan múltiples series, mientras otros han mostrado que los programas que utilizan múltiples series obtienen incrementos superiores. Las discrepancias en los resultados pueden venir explicadas por las distintas características de los sujetos a los que se les somete al entrenamiento de la fuerza. Esto significa que es probable que las personas principiantes respondan de manera favorable a una o múltiples series por ejercicio, especialmente durante las semanas iniciales de entrenamiento, mientras que en las personas entrenadas los programas que utilizan múltiples series sean los que proporcionan mejoras superiores en el desarrollo de la fuerza.

Estudios más recientes revelan que la capacidad de adaptación con el entrenamiento de fuerza parece ser menor en las personas mayores que en los jóvenes (Lemmer *et al.* 2001). Así mismo, cuando la intensidad y o la frecuencia de entrenamiento aumenta, disminuye la capacidad de adaptación en la mejora de la fuerza, especialmente en los grupos de edad avanzada (Hakkinen *et al.* 1998). En consecuencia, es posible que con personas mayores y especialmente los más frágiles se deba ser más conservador en la progresión de las diferentes variables relacionadas con el entrenamiento (volumen, intensidad y frecuencia) y que los diseños de entrenamiento deban ser diferentes a los utilizados con personas más jóvenes. El Colegio Americano de Medicina del Deporte (1998) sugiere que en personas de mediana edad y edad avanzada, el entrenamiento de fuerza para mejorar la condición física general debe realizarse con una frecuencia de 2-3 sesiones por semana aunque no hace una referencia específica para el anciano frágil. En esta línea, considera que una serie de entrenamiento es más eficaz que múltiples series ya que permite mejorar la fuerza casi en igual magnitud que un entrenamiento con múltiples series (Kraemer *et al.* 2004). Este tipo de programas necesitan menos tiempo para su realización y producen beneficios similares sobre la salud y el estado de forma en personas mayores previamente inactivas. Las recomendaciones de la Sociedad Americana de Geriatría (American Geriatrics Society Panel on Exercise and Osteoarthritis 2001) y de la Sociedad Americana del Corazón (Williams *et al.* 2001) tampoco son específicas para el anciano frágil.

En resumen, las recomendaciones realizadas en la actualidad por algunas instituciones y autores en el ámbito del entrenamiento de fuerza y potencia muscular, se alejan de la realidad. Este tipo de recomendaciones suelen ser demasiado intensas y fatigantes y pueden inducir un aumento del riesgo de lesión y sobreentrenamiento, además de no favorecer en mayor medida el desarrollo de la fuerza y masa muscular que los efectos que pudieran surtir de utilizar intensidades inferiores. La creencia más generalizada, especialmente en la literatura científica americana, es que para mejorar la fuerza máxima hay que realizar repeticiones por serie hasta el fallo (p.e. 8/10/12 repeticiones máximas RM). Sin embargo, diferentes estudios muestran que realizar repeticiones hasta el fallo no es necesario y puede incluso producir sobreentrenamiento y lesiones por sobrecarga (Izquierdo *et al.* 2004; Izquierdo *et al.* 2010; Izquierdo *et al.* 2006). Como aplicación práctica de estos trabajos se sugiere que el entrenamiento de fuerza, cuando se realiza en personas sedentarias o de edad avanzada, especialmente si son frágiles, debería comenzar realizando 8-10 repeticiones por serie con un peso que pudiésemos realizar 20 repeticiones máximas (20 RM) o más y no sobrepasar la realización de 4-6 repeticiones por serie con un peso que pudiésemos realizar 15 RM.

Entrenamiento combinado de fuerza y resistencia

Durante las últimas décadas se ha prestado una especial atención a la combinación del entrenamiento de fuerza muscular y resistencia aeróbica. Los resultados de estos trabajos muestran que entrenamientos de 10 a 12 semanas de duración, con una frecuencia semanal comprendida entre 4 y 11 sesiones, a intensidades comprendidas entre el 60 y el 100% de VO2 máx en bicicleta, y a intensidades comprendidas entre el 40 y el 100% de 1 RM en el trabajo de fuerza, se acompañaron de un aumento del 6 al 23% del VO2 máx y del 22 al 38% de la fuerza máxima (Leverit *et al.* 1999). En la mayoría de estos trabajos, la magnitud del incremento observado en la fuerza máxima del miembro inferior fue superior en el grupo que realizaba exclusivamente el entrenamiento de fuerza máxima, que la observada en el grupo que realizaba un programa combinado de fuerza y resistencia aeróbica. Los mecanismos que pueden explicar la inhibición del desarrollo de la fuerza muscular después de participar en un programa combinado de fuerza y resistencia, en comparación cuando sólo se realiza un programa de entrenamiento de fuerza, no están del todo definidos aunque se postulan determinadas hipótesis como el sobreentrenamiento y la falta de adaptación metabólica y morfológica del músculo esquelético al entrenamiento combinado (Kraemer *et al.* 1995).

En ancianos y particularmente en frágiles, son poco conocidos los efectos de un programa combinado de fuerza y resistencia aeróbica. La mayoría de estos trabajos se han realizado en ancianos sanos y muestran que las mejoras observadas en la fuerza máxima del miembro inferior en el grupo que realiza un entrenamiento exclusivo de fuerza no son diferentes a las observadas en el grupo que realiza un programa combinado de fuerza y resistencia (Izquierdo *et al.* 2004). No obstante, recientemente estudios realizados en población frágil que combinan actividad aeróbica y ejercicio de fuerza, han demostrado mejorías en los parámetros funcionales de la fragilidad tales como la velocidad de la marcha y SPPB (Binder *et al.* 2004; Pahor *et al.* 2006).

La mayoría de los trabajos que han estudiado los efectos de un programa combinado de fuerza y resistencia lo han realizado examinando el efecto de la combinación de ambas cualidades (fuerza y resistencia) en la misma sesión, sin embargo no se conocen estudios que hayan analizado el efecto de sustituir una sesión de fuerza por una de resistencia o viceversa. En un trabajo realizado en nuestro laboratorio se examinó en 31 hombres sanos (65-74 años) el efecto del entrenamiento (2 veces por semana durante 16 semanas) exclusivo de fuerza (S), exclusivo de resistencia (E) o combinado (SE) (1 sesión/semana S + 1 sesión/semana E) sobre la fuerza máxima del miembro inferior, el área de sección transversal del cuádriceps femoral y la potencia máxima alcanzada durante un test progresivo hasta el agotamiento en cicloergómetro (WL máx). La fuerza de la extremidad inferior y el área de sección transversal del cuádriceps femoral en S (41 y 11%, respectivamente) y SE (38 y 11%, respectivamente) fueron mayores que los registrados en E (11 y 4%, respectivamente). Los aumentos observados en WL máx fueron mayores en SE (28%) y E (23%) que en S (10%). Un resultado interesante de este trabajo fue la ausencia de diferencias significativas entre el entrenamiento exclusivo de fuerza y el entrenamiento combinado en los incrementos de fuerza y área de sección transversal. El incremento de potencia máxima en el test incremental fue similar con el entrenamiento exclusivo de resistencia y el entrenamiento combinado. Estos resultados sugieren que un programa de entrenamiento combinado de fuerza y resistencia en personas mayores produce incrementos similares en la fuerza y la masa muscular que un programa exclusivo de entrenamiento de fuerza e incrementos similares en la potencia máxima aeróbica que los cambios producidos por un programa exclusivo de entrenamiento de la resistencia cardiovascular (Izquierdo *et al.* 2004).

Programa de ejercicio físico multicomponente

Tradicionalmente se conoce a los programas que engloban ejercicios de resistencia, flexibilidad, equilibrio y fuerza. Existen dos revisiones sistemáticas recientes que analizan el beneficio de estos programas en frágiles. En la revisión de Chin *et al.* (2008) examinaron el efecto del ejercicio en la capacidad funcional de los ancianos frágiles. Su conclusión principal es que tanto los programas de fuerza como los multicomponentes eran intervenciones que mejoraban la capacidad funcional de esta población. Posteriormente Daniels *et al.* (2008) analizaron las intervenciones que prevenían discapacidad en ancianos frágiles de la comunidad. Los estudios de intervención de ejercicio revisados mostraron una mayor superioridad de los programas multicomponentes frente al entrenamiento de fuerza aislado de la extremidad inferior, particularmente en los moderadamente frágiles. Aquellas intervenciones cuya duración era mayor (>5 meses), con una frecuencia de 3 veces por semana, 30-45 minutos – sesión, parece que mostraban una mayor beneficio en términos funcionales. Hay que destacar que de los 4.062 estudios seleccionados sólo 10 cumplieron criterios de inclusión por problemas metodológicos en cuanto a criterios de inclusión, fundamentalmente porque no se especificaba qué criterios usaban para definir fragilidad.

Efectos del ejercicio físico sobre los dominios de la fragilidad

El principal evento adverso de la fragilidad es el deterioro funcional y la discapacidad y dependencia (Fig. 1). Como ya ha quedado reseñado en diversos estudios epidemiológicos (Miller *et al.* 2000; Wu *et al.* 1999) la práctica regular de ejercicio físico se asocia con una disminución del riesgo de discapacidad para ABVD. No obstante, todavía no está del todo aclarado si la actividad física puede prevenir o revertir la fragilidad. En un reciente estudio observacional (Peterson *et al.* 2009) llevado a cabo en 2.500 ancianos (donde se definió fragilidad por una Velocidad de la Marcha (VM) <0,6 m/s y la incapacidad de levantarse sin ayuda una la silla) observaron que aquellos ancianos con una actividad física regular, tenían menor probabilidad de desarrollar fragilidad. Además, existía 3 veces más probabilidad de presentar fragilidad severa en sedentarios frente activos. La transición desde estadios leves de fragilidad a estadios severos era mucho más frecuente en sedentarios.

Actualmente el concepto de fragilidad es muy amplio y dinámico (Fig. 1) y engloba otros dominios que están interrelacionados tanto en su etiopatogenia como en su vulnerabilidad para padecer eventos adversos. Cabe destacar los siguientes, en los que el ejercicio físico puede constituir una intervención predominante:

• Caídas. Habitualmente interrelacionadas con el síndrome de fragilidad constituyendo un motivo de consulta y evento adverso extraordinariamente frecuente en el paciente frágil. Su abordaje resulta complejo y las intervenciones habitualmente deben ser multifactoriales. El ejercicio físico quizás sea la intervención más probada y testada en la prevención de caídas. Es conocido que resulta eficaz para reducir el riesgo y la tasa de caídas tanto en población comunitaria como residencial (Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society 2011; Gillespie *et al.* 2009). Los ejercicios en grupo multicomponente (equilibrio, fortalecimiento, fuerza y resistencia) y el Tai Chi como ejercicio grupal parecen reducir la tasa y el riesgo de caídas y son especialmente beneficiosos en población anciana frágil con caídas (Gates *et al.* 2008).

• Deterioro cognitivo. La relación entre el deterioro cognitivo y la fragilidad es íntima y probablemente biyectiva, ya que comparten bases fisiopatológicas comunes y resultados a corto y medio plazo (hospitalización, caídas, discapacidad, institucionalización y mortalidad) (Garcia-Garcia *et al.* 2011). Esta relación se pone de manifiesto porque probablemente el sistema nervioso central y muscular comparta vías patogénicas comunes en el devenir de la discapacidad. En el estudio Toledo de envejecimiento y fragilidad (Garcia-Garcia *et al.* 2011), se ha observado como el deterioro cognitivo y la fuerza mantienen un relación directamente proporcional. La demencia comparte parcialmente los síntomas que forman parte del fenotipo de fragilidad como es la disminución de la velocidad de la marcha y la disminución de la actividad. Algunos autores consideran que incluso ambos síndromes se pueden englobar dentro de una misma entidad clínica. En este sentido tiene lógica que aquellas intervenciones que resultaran eficaces en el paciente frágil pudiesen ser beneficiosas en el anciano con deterioro cognitivo y viceversa. Estudios recientes, como el de Liu-Ambrose *et al.* (2010), han demostrado cómo programas de ejercicio de resistencia semanales durante 12 semanas, en una cohorte de ancianas, no solo provocan aumentos de la velocidad de la marcha, sino que resultan beneficiosos en la mejoría de funciones cognitivas ejecutivas, que están interesantemente relacionadas con el riesgo de caída (Casas-Herrero, Montero-Odasso 2010). De tal forma que, un posible mecanismo que explique la disminución del riesgo de caída en pacientes frágiles con deterioro cognitivo, puede radicar en la mejoría de las funciones ejecutivas mediada por el ejercicio físico. En un análisis secundario, este grupo de autores han corroborado esta hipótesis (Liu-Ambrose *et al.* 2010), mostrando cómo mejorías en la función ejecutiva se asocian con incrementos en la velocidad de la marcha y en la fuerza muscular del cuádriceps.

• Depresión. Es incluida por muchos autores dentro del espectro de la fragilidad. El fenotipo de fragilidad descrito por Fried (pérdida de peso no intencionada, debilidad, disminución de actividad física, cansancio, lentitud) puede ser típico de un cuadro depresivo del anciano. Además también comparten bases etiopatogenias inflamatorias-inmunológicas (Katz 2004). Es conocido que el ejercicio físico mejora los síntomas depresivos a corto plazo, fundamentalmente en aquellos que están ya deprimidos (Bartholomew *et al.* 2005). No obstante, sus efectos a largo plazo sobre síntomas depresivos y ansiosos en ancianos frágiles queda por clarificar en ensayos clínicos. Una de las posibles hipótesis que explica este potencial efecto antidepresivo y ansiolítico radica en las propiedades antiinflamatorias del ejercicio físico (Nicklas *et al.* 2008).

Entre los problemas frecuentes del ejercicio físico en ancianos frágiles, se encuentran los relacionados con la comorbilidad, aspecto que con gran frecuencia está presente y se correlaciona con el síndrome de la fragilidad. Por sí misma no contraindica un programa de ejercicio pero sí requiere una evaluación médica cuidadosa previa al comienzo del programa. En general las contraindicaciones absolutas suelen ser cardiovasculares (infarto cardiaco reciente o angina inestable, hipertensión no controlada, insuficiencia cardiaca aguda y bloqueo AV completo) (Landi *et al.* 2010).

Los principales riesgos del entrenamiento aeróbico y de fuerza se resumen en la Tabla 1 donde se muestran principios generales, recomendaciones, beneficios y riesgos de ambos programas de ejercicio. Como se ha señalado previamente, en población anciana frágil se recomiendan programas más conservadores en cuanto a intensidades, potencia, volumen y frecuencia de entrenamiento. Cuanto más gradual sea la progresión mejor será la tolerancia y se minimizarán efectos secundarios. Hay que tener en cuenta que en muchos estudios no se señalan adecuadamente la aparición de efectos secundarios (Liu *et al.* 2009). Por último, es destacable la adherencia como un problema muy habitual en los programas de ejercicio en ancianos frágiles que habitualmente no han realizado actividad física previa. Generalmente es mejor en ejercicios aeróbicos (caminar, bicicleta) frente a programas de fuerza y en ejercicios grupales frente a los realizados en domicilio.

Tabla 1. Principios generales, recomendaciones, beneficios y riesgos de un programa de entrenamiento aérobico y de fuerza (Adaptada de Landi et al. 2010).

	Entrenamiento aeróbico	Entrenamiento de fuerza
Principios generales	Grandes grupos musculares Muchas repeticiones Baja resistencia	Contracción varios grupos musculares Pocas repeticiones Moderada-alta resistencia
Recomendaciones	Ejercicio aeróbico bajo impacto Comienzo baja intensidad y corta duración (5 minutos) Calentamiento y estiramiento	Medir fuerza y potencia basal Carga inicial 40-50% Grandes músculos pareados (ag-antag) Pequeños incrementos carga
Beneficios	CV, composición corporal, metabólico Resistencia muscular Comorbilidad	↑ fuerza, potencia, masa muscular magra Rango de movilidad (flexibilidad) Función física
Riesgos	Evento cardiaco Daño musculoesquelético	Lesión muscular Fracturas, exacerbación enf. articular

En resumen, de manera general, la práctica de ejercicio físico es la intervención más eficaz para retrasar la discapacidad y los eventos adversos que asocia habitualmente el síndrome de la fragilidad. El entrenamiento de fuerza, en particular, cada vez tiene más resultados favorables en este grupo poblacional y sus efectos son más destacados en otros dominios del síndrome como las caídas y el deterioro cognitivo. En la actualidad, son necesarios más estudios aleatorizados que aclaren la utilización óptima de los componentes de un programa de fuerza y si éstos resultan más beneficiosos en términos funcionales que los multicomponente. En este contexto, se recomienda desarrollar guías clínicas específicas para pautar ejercicio físico en el anciano frágil.

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3. EXPERIMENTAL STUDIES

3.1 Hypothesis

H1. Frail and mild cognitive decline institutionalized aged participants share functional and adverse outcomes. However, we hypothesize that subtle difference in functional parameters would help to distinguish frail aged participants with and without mild cognitive decline (Study I).

H2. A multicomponent exercise program that includes power training is an effective strategy in the functional capacity´s improvement of a very old cohort of frail institutionalised participants. We speculate that this program would modify muscle mass area and muscle fat infiltration assessed with computed tomography (Study II).

H3. A multicomponent exercise intervention that includes resistance training as an essential component of the intervention is an effective strategy to improve functional capacity of institutionalized frail participants with dementia after long-term use of physical restraints. We speculate a decline in the functional capacity after training cessation (Study III).

3.2 Objectives

O1. To compare the muscle mass, strength, and functional performance between the frail elderly with and without MCI using functional tests with dual task paradigm. To help understand the possible differences between these two frail groups, we compared them with a group of age-matched elderly subjects without frailty. A second objective was to investigate the associations between functional capacity and muscle strength, power, and mass in the frail elderly (Study I).

O2. To investigate the effects of multicomponent exercise intervention, composed of high-speed power resistance training, balance, and gait exercises, on muscle strength and power variables, thigh cross-sectional area (CSA), muscle attenuation, incidence of falls, and functional outcomes such as dual-task performance in institutionalised frail nonagenarians (Study II).

O3. To investigate the effects of an 8 week multicomponent exercise intervention on physical function in older patients with dementia after long-term physical restraint.

After a follow-up period of 12 and 24 weeks of training cessation, we investigated the sustainability of the physical gains (Study III).

3.3 METHODS

3.3.1 Study I

3.3.1.1 Subjects and experimental design:

The participants were institutionalized oldest old patients from the Pamplona (Spain) area older than 75 years old. They were included in the three groups (non-frail without MCI, frail without MCI and frail with MCI) of the study according to the Fried criteria of frailty or robustness (Fried *et al.* 2001) and the MCI consensus definition provided by Windbland *et al.* (2004). The Fried criteria of frailty were determined by the presence of three or more of the following components: slowness, weakness, weight loss, exhaustion, and low physical activity (Fried *et al.* 2001). The specific recommendations for the general MCI criteria include the following: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired (Windbland *et al.* 2004). Participants fulfilled the criteria for MCI if they had a subjective memory complaint, a report of cognitive deterioration from the patient and/or family, objective memory impairment in cognitive tests with the absence of significant functional impairment, and the absence of clinical dementia. Exclusion criteria included dementia, disability (defined as a Barthel index lower than 60), and the inability to walk independently. An age-matched non-frail group was included for physical and functional comparisons. Fifty-six elderly subjects volunteered to take part in this study, completed an ethical consent form, and met the necessary requirements to join the study. After completing the clinical and cognitive evaluations, 43 elderly men and women were finally included into any of the three groups: the frail without MCI group (93.4±3.2 years); the frail with MCI group (frail+ MCI) (age: 92.4±4.2 years), and the non-frail group (age: 88.2±4.1 years). The complete physical characteristics of the participants are presented in the table 2. Women accounted for 67% of the patients (9 of 13, 14 of 20 and 6 of 10 in the frail + MCI, frail and non frail groups, respectively). For the muscle mass comparisons, only the frail elderly (with and without MCI) were assessed. A subset of frail subjects (n=13) had their 1RM strength and muscle power measured in the leg press machine to investigate the associations between these variables with functional capacity. All subjects or their legal guardians agreed with their participation in the trial and completed an ethical consent form. The study was conducted according to the Declaration of Helsinki, and was approved by the Ethics Committee of the Public University of Navarra, Spain.

Table 2: Physical characteristics. Mean ± SD.

	Frail + MCI (n=13)	Frail (n=20)	Non-frail (n=10)
Age (years)	92.4 ± 4.2	93.4 ± 3.2	88.2 ± 4.1
Women/men	9/4	14/6	6/4
Body mass (kg)	60.8 ± 7.7	52.3 ± 12.7	60.5 ± 7.8
Height (cm)	154.3 ± 6.8	151.8 ± 11.7	152.2 ± 2.2
Body mass index ($kg.m^{-2}$)	24.7 ± 3.8	21.4 ± 3.8	28.3 ± 4.7†
Schooling level			
Basic uncompleted	2	5	2
Basic completed	8	11	6
High School completed	2	3	1
College complete	1	1	1
MEC	23.0 ± 2.5*	28.8 ± 2.9	31.0 ± 2.6

MEC, Mini-Examen Cognoscitivo. *Significant difference from frail and non-frail groups (P <0.001). †Significant difference from frail group (P <0.01).

In order to investigate the possible differences and similarities in functional outcomes, muscle fat infiltration and power output between frail elderly with and without MCI we designed a cross-sectional study to compare three groups of elderly populations: frail, frail+ MCI, and age-matched non-frail elderly. In addition, we assessed the associations between skeletal muscle strength, power, and mass with functional capacity in the frail group to help identify the most relevant physical outcomes needed to prevent disability. Physical evaluations were performed using dynamometry, functional tests (including strength, gait, and balance tests), and computed tomography (CT) of the thigh muscles. Study participants were assessed in their institution on different occasions and were transported to the hospital for the CT assessments. Prior to data collection, the participants took part in a familiarization procedure for each test.

3.3.1.2 Functional outcomes

The gait velocity was assessed using the 5-meter habitual gait velocity test (GVT) and TUG test. Starting and ending limits were marked on the floor with tape lines for a total distance of 7 meters. The first and last meter, considered the warm-up and the deceleration phases, respectively, were not included in the calculations for the gait assessment. The TUG test consisted of measuring the time to perform the task of standing up from a sitting position in a chair, walking three meters, turning, returning to the chair and sitting down. The dual-task paradigm was used in the 5-meter habitual GVT and the TUG test. Two trials were used to measured gait velocity while performing a verbal or counting task (verbal GVT and counting GVT, respectively). During the verbal fluency dual-task condition (verbal GVT), we measured the gait velocity while participants were naming animals aloud; during the arithmetic dual-task condition (counting GVT), we measured gait velocity while participants were counting backward aloud from one hundred by ones. The velocity and time were measured, and the cognitive score was measured by counting the number of animals named (dual-task with verbal performance) or counting the numbers backward (dual-task with arithmetic performance). Balance was assessed using the FICSIT-4 tests of static balance: the parallel, semi-tandem, tandem, and one-legged stance tests. The subjects progressed to the hardest test regardless of their success in the easier tests. The ability to stand up from a chair without support (rise from a chair test) was assessed, and the score was determined by the maximum number of rises that the subject was able to complete in 30 seconds. Data on the incidence of falls were obtained using questionnaires.

3.3.1.3 Maximal strength and muscle power

Upper (right hand grip) and lower limb (right knee extensors and hip flexors) isometric muscle strength was measured using a manual dynamometer. Maximal dynamic strength was assessed using the 1RM test on the bilateral leg press exercise. The bilateral leg press 1RM was performed using an exercise machine (Exercycle, S.L., BH Group, Vitoria, Spain). On the day of the test, the subjects warmed up with specific movements for the exercise test. Each subject's maximal load was determined with a maximum of five attempts with a 4-min recovery between attempts. After determination of the 1RM values, subjects performed three repetitions at maximal velocity at intensities of 30% and 60% of the 1RM to determine the maximal and mean power and the maximal and mean velocities at these intensities. Two attempts were performed at each intensity, with 2 min of recovery between attempts. During the bilateral leg press actions at the different intensities (30%–60% of 1RM), bar displacement, average velocity ($m \cdot s^{-1}$), and mean power (W) were recorded by linking a linear velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain).

3.3.1.4 Muscle-cross sectional area

The midthigh lower-extremity muscle of the left quadriceps femoris was assessed using a 64-row CT scanner (SIEMENS DEFINTION AS, Erlangen, Germany). The cross sectional area (CSA) of the subcutaneous adipose tissue (SAT), intermuscular adipose tissue (IMAT); quadriceps femoris (QF) muscle; adductor muscles including the adductor longus and magnus; and flexor muscles, including the semitendinous, semimembranosus, and biceps femoris, were measured. The scans were later analyzed for the CSA (mm^2) of adipose tissue and muscle tissue. Image segmentation of adipose tissue and skeletal muscle CSAs of the abdominal and thigh images was performed using commercially available software (Slice-O-Matic, Tomovision, Montreal, Canada), as previously reported.(Santanasto *et al.* 2011). The boundaries of the adipose and muscular compartments measured were depicted using a manual cursor. The mean attenuation coefficient values of adipose and muscle within the regions outlined on the images were determined by averaging the CT number (pixel intensity) in Hounsfield units (HU). Skeletal muscle and adipose tissue areas were calculated by the range of attenuation values for skeletal muscle (0-100 HU), high-density muscle (HDM) (30-100 HU), low-density muscle (LDM) (0-29 HU), and adipose (–190 - –30 HU) tissue (Ross 2003).

3.3.1.5 Cognitive Test

Objective memory impairment was operationalized by the demonstration of memory impairment by neuropsychological testing. For this purpose it was used "MEC test (Mini-Examen Cognoscitivo), an adaptated Spanish validated version for geriatric population of MMSE (Lobo *et al.* 1979) with a sensibility of 90.7%, and a specificity of 69%. It includes two more items than MMSE. Maximal score is 35 and cut off point for cognitive decline is below 28.

3.3.1.6 Statistical analysis

Descriptive results are reported as the mean ± SD. The SPSS statistical software package (version 17.0) was used to analyze all data. Normal distribution and homogeneity parameters were verified with Shapiro-Wilk and Levene tests, respectively. The differences between groups were assessed using a one-way analysis of variance (ANOVA) with Tukey post-hoc tests. Retrospective analysis provided using the GPOWER program (version 3.1.7) determined that the number of participants in each group provided a statistical power of over 80% to the differences detected in all variables. Exceptions were observed in the balance and incidence of falls, which the retrospective statistical power was 75%. The Pearson product moment correlation test was used to investigate possible associations between the variables. In the non-parametric data, a Spearman correlation test was used. Significance was defined as $P<0.05$.

3.3.2 Study II

3.3.2.1 Subjects and experimental design

The participants were institutionalised oldest old patients from the Pamplona (Spain) area and were included in the study if they were 85 years or older and met Fried's criteria for frailty, which was determined by the presence of three or more of the following components: slowness, weakness, weight loss, exhaustion, and low physical activity (Fried *et al.*. 2001). Before the study, all participants underwent a medical assessment. The exclusion criteria were the absence of frailty or pre-frailty syndrome, dementia, disability (defined as a Barthel Index (BI) lower than 60 and inability to walk independently without help of another person), recent cardiac arrest, unstable coronary syndrome, active cardiac failure, cardiac block or any unstable medical condition. Of the 39 elderly who were approached, 32 agreed to participate in the trial. From the initial sample of 32 oldest old who volunteered to take part in this study and met the inclusion criteria, 24 elderly men and women completed the pre- and post-measurements. Five subjects died during the study from causes that were unrelated to the exercise intervention, and three subjects dropped out due to medical complications. Figure 3 shows the participants flow diagram. Women accounted for 70% of the patients (17 of 24, 8 and 10 in the intervention and control groups, respectively). Subjects were randomised into two groups: an exercise group (age: 93.4±3.2 years; n=11) and a control group (age: 90.1±1.1 years, n=13). This procedure was established according to the "CONSORT" statement, which can be found at: http://www.consort-statement.org/. Both groups were assessed for all the functional outcomes, dual-task performance, incidence of falls, isometric strength, muscle mass, and muscle attenuation. However, only the exercise intervention group underwent the one-repetition maximum (1RM) strength and muscle power measurement in the leg press machine. The study was conducted according to the Declaration of Helsinki, and the protocol was approved by the local Institutional Review Board.

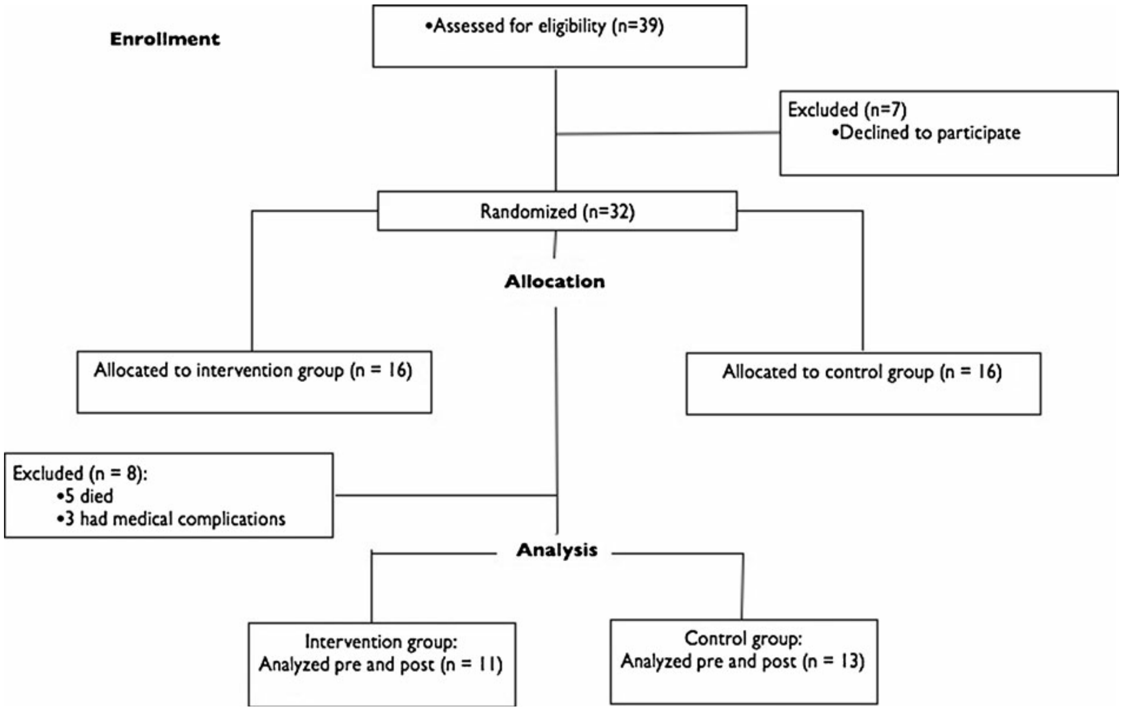

Figure 3. Flowchart for screening, recruitment, allocation, and intervention

This randomised controlled trial was designed to investigate the effects of multicomponent exercise intervention, composed of high-speed power resistance training, balance, and gait exercises, on muscle strength and power variables, thigh CSA, muscle attenuation, incidence of falls, and functional outcomes such as dual-task performance in institutionalised frail nonagenarians. The exercise intervention lasted for 12 weeks. Prior to data collection, the participants took part in a familiarisation procedure for each test. We have previously tested the stability and reliability of these variables in a similar population. Both before and after the intervention, each specific test was overseen by the same investigator, who was blinded to the training group of the subjects, and was conducted on the same equipment with identical subject/equipment positioning. The randomisation sequence was generated by http://www.randomization.com and concealed until interventions were assigned. Each subject performed the tests at the same time of day throughout the study.

3.3.2.2 Functional outcomes

Gait ability was assessed using 5-m habitual gait and TUG tests. In the 5-m habitual gait test, subjects were asked to walk at their habitual speed on a flat course of 5 m with an initial distance of 2 m of acceleration before, which was not included in the calculations of gait assessment. The TUG test consisted of counting the time to perform the task of standing from a chair, walking at 3 m, turning, going back, and sitting down on the same chair. In addition, dual-task performance was assessed with verbal and arithmetic methods in the 5-m habitual gait and TUG tests. The dual-task paradigm was used in the 5-m habitual GVT and the TUG test. Two trials were used to measured gait velocity while performing a verbal or counting task (verbal GVT and counting GVT, respectively). During the verbal fluency dual-task condition (verbal GVT), we measured the gait velocity while participants named animals aloud; during the arithmetic dual-task condition (counting GVT), we measured the gait velocity while participants counted backward aloud from 100 by ones. Balance was assessed using the FICSIT-4 tests of static balance (parallel, semitandem, tandem, and one-legged stance tests), and the subjects progressed to the hardest test only if they had success in the easiest. Moreover, the rise from a chair test was assessed and consisted of determining the most rises that the subjects were able to do in 30 s. The functional outcomes have been described in details elsewhere (Casas-Herrero *et al.* 2013). Data on the incidence of falls were assessed retrospectively using questionnaires to residents. Falls were defined as events in which the participant unintentionally came to rest on objects (i.e. person, table, or chest of drawers) that prevented the center of mass from exceeding the base of support or came to rest on the floor or a lower object because the center of mass exceeded the base of support (Wolf *et al.* 1996). Functional status was assessed before measurements with the BI, an international and validated tool of disability. The values ranged from 100 (complete independence for daily living activities) to 0 (severe disability). We considered a significant functional decline if the BI decreased over ten points after the last measurement.

3.3.2.3. Maximal isometric and dynamic strength and muscle power

Isometric upper (right hand grip) and lower limb (right knee extensors and hip flexors) muscle strength was measured using a manual dynamometer. Maximal dynamic strength was assessed using the 1RM test in the bilateral leg press and bench press exercises. The bilateral leg press and bench press 1RM were performed using exercise machines [Exercycle, S.L. (BH Group), Vitoria, Spain]. On the test day, the subjects warmed up with specific movements for the exercise test. Each subject's maximal load was determined with no more than five attempts, with a 3-min recovery between attempts. After determination of the 1RM values, the subjects performed three repetitions at maximal velocity at intensities of 30 and 60 % of 1RM to determine the maximal power at these intensities. Two attempts were performed at each intensity level, with a 2-min recovery between attempts. During the bilateral leg press, with actions at different intensities (30 to 60 % of 1RM), the bar with the maximal power (W) was recorded by connecting a velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain). For all neuromuscular performance tests, a strong verbal encouragement was given to each subject to motivate them to perform each test action as maximally and as rapidly as possible.

3.3.2.4 Muscle cross sectional area and quality

Muscle CSA and muscle tissue attenuation (indicative of fat infiltration) were determined using computed tomography scans at the midthigh of the left quadriceps femoris using a 64-row CT scanner (Siemens Definition AS, Erlangen, Germany). The midthigh femur level was defined as the midpoint between the superior aspect of the left femoral head and the inferior aspect of the left lateral condyle. To locate the midpoint, an anterior–posterior scan of the entire femur was obtained. The CSAs of QF muscle; adductor (ADD) muscles including the adductor longus and magnus; and knee flexor (KF) muscles, including the semitendinosus, semimembranosus and biceps femoris, were measured. The scans were later analyzed for the CSA (mm^2) of the adipose tissue and muscle tissue. Image segmentation of the adipose tissue and skeletal muscle CSAs of the thigh images was performed using commercially available software (Slice-O-Matic, Tomovision, Montreal, Canada), as previously reported (Santanasto *et al.* 2011). The boundaries of the adipose and muscular compartments measured were depicted using a manual cursor. The mean attenuation coefficient values of adipose and muscle within the regions outlined on the images were determined by averaging the CT number (pixel intensity) in HU. Muscle cross sectional and muscle tissue attenuation were calculated using the range of attenuation values for skeletal muscle (0–100 HU), high-density muscle (30–100 HU), low density muscle (0–29 HU), and adipose tissue (−190 to −30 HU) (Ross 2003).

3.3.2.5 Exercise intervention

Before the exercise intervention, the participants were carefully familiarized with the training procedures. Participants underwent a twice-weekly, 12-week multicomponent exercise program composed of upper and lower body resistance training with progressively increased loads that optimized the muscle power output in this population (8–10 repetitions, 40–60 % of 1RM) using resistance variable machines [Exercycle, S.L. (BH Group), Vitoria, Spain] combined with balance and gait retraining exercises that progressed in difficulty and functional exercises, such as rises from a chair. A minimum of 2 days elapsed between consecutive training sessions. The resistance exercises focused on the major upper and lower limb muscles.

Each resistance training session included two exercises for the leg extensor muscles (bilateral leg extension and bilateral knee extension muscles) and one exercise for upper limbs (seated bench press). During the progressive resistance training, instruction was provided to the participants to perform the exercises at a high velocity of motion. However, care was taken to ensure that the exercises were executed in the correct form. In each session, subjects performed a specific warm-up with one set of very light loads for the upper and lower body. Balance and gait retraining exercises that progressed in difficulty were also implemented: semitandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (foam pads sequence), and altering the base of support and weight transfer from one leg to the other. All training sessions were carefully supervised by one experienced physical trainer. The training sessions lasted for approximately 40 min. The approximate duration of each part of the training was 5 min of warm-up, 10 min balance and gait retraining, 20 min of resistance training, and 5 min of stretching (cool-down). To reduce the participant dropout, music was played during all sessions, and adherence of more than 90 % was observed in all subjects. Sessions were deemed completed when at least 90 % of the prescribed exercises had been successfully performed.

3.3.2.6 Control group activities

During the intervention period, subjects in the control group performed mobility exercises 30 min per day, at 4 days per week, which consisted of small active and passive movements applied as a series of stretches in a rhythmic fashion to the individual joints. Such exercises are routinely encouraged in most Spanish nursing homes.

3.3.2.7 Statistical analysis

The SPSS Statistical Software package (version 17.0) was used to analyze all data. Normal distribution and homogeneity parameters were evaluated with the Shapiro–Wilk and Levene's tests, respectively. The results were reported as mean ±SD. The training related effects were assessed using a two-way analysis of variance with repeated measures (group×time). When the interaction was significant, the main factors' group and time were tested again using t tests. The statistical power observed ranged from 0.85 to 1.00 for all variables analyzed. Significance was accepted when $P<0.05$.

3.3.3 Study III

3.3.3.1 Subjects and experimental design

The participants were institutionalized elderly patients from the Tudela (Spain) area and were included in the study if they met the following criteria: age 75 years or older, diagnosis of dementia, several months of physical restraint and fulfillment of Fried's criteria for frailty, which was determined by the presence of three or more of the following components: slowness, weakness, weight loss, exhaustion and low level of physical activity (Fried *et al.* 2001). In the individuals who met the inclusion criteria for cognitive impairment (MMSE score of 17-26) (Hauer *et al.* 2012; Hueger *et al.* 2009) a dementia diagnosis was confirmed according to the international standards for Alzheimer's disease, multifactorial cause, or vascular dementia. The diagnosis was based on medical history, clinical examination, cerebral imaging, an established neuropsychological test battery [Consortium to Establish a Registry for

Alzheimer's Disease (CERAD)], the Trail-Making Test(Hueger *et al.* 2009) and a Clinical Dementia Rating (CDR) (Morris 1993) at least of 1 thus allowing a diagnosis of different types of dementia. Before the study, all of the participants underwent a medical assessment. Physical restraint was defined as any limitation of an individual's freedom of movement (Hantikainen 1998; Hammers *et al.* 2005), including restraints those worn by the person (belt, chest and arm/leg) and those attached to beds (full-enclosure bed rails) or chairs (locked table)(Gulpers *et al.* 2010). All of the patients had experienced at least 9 months of physical restraint (14 ± 3 months). The exclusion criteria were the absence of frailty, recent cardiac arrest, unstable coronary syndrome, active cardiac failure, cardiac block or any unstable medical condition. Of the 29 frail elderly patients with dementia who were approached, 21 patients with the approval of their legal guardians agreed to participate in the trial after completing an informed consent form. From the initial sample of 21 elderly patients who volunteered to take part in this study and who met the inclusion criteria, 18 (age of 88.1 ± 5.1 years; n = 18) completed the pre- and post-training measurements. During the intervention, one subject died of causes unrelated to the exercise intervention, and two participants dropped out of the study because of medical complications. During the follow-up period, 11 participants completed the physical evaluations at 12 and 24 weeks after the cessation of the exercise intervention. Six participants died during the follow-up and one dropped out of the study because of a medical complication (Figure 4). Dementia was caused by Alzheimer's disease in most of the patients (10 of 18), but vascular disease (1 patient) and a multifactorial cause (7 patients), primarily Alzheimer's disease with a vascular component, were also present. In addition to frailty and dementia, several comorbidities were diagnosed with a mean of "n" diagnosed per patient. The most usual comorbidities were type II diabetes (7 patients), chronic renal failure (7 patients), hypertension (6 patients), depression (4 patients), osteoporosis (4 patients), ischemic heart disease (3 patients), dyslipidemia (3 patients) and osteoarthritis (3 patients). Women accounted for 55% of the patients with dementia (10 of 18 patients). The patients were assessed for all of the functional outcomes, dual-task performance and muscle strength. The study was conducted according to the Declaration of Helsinki, and the protocol was approved by the local Institutional Review Board.

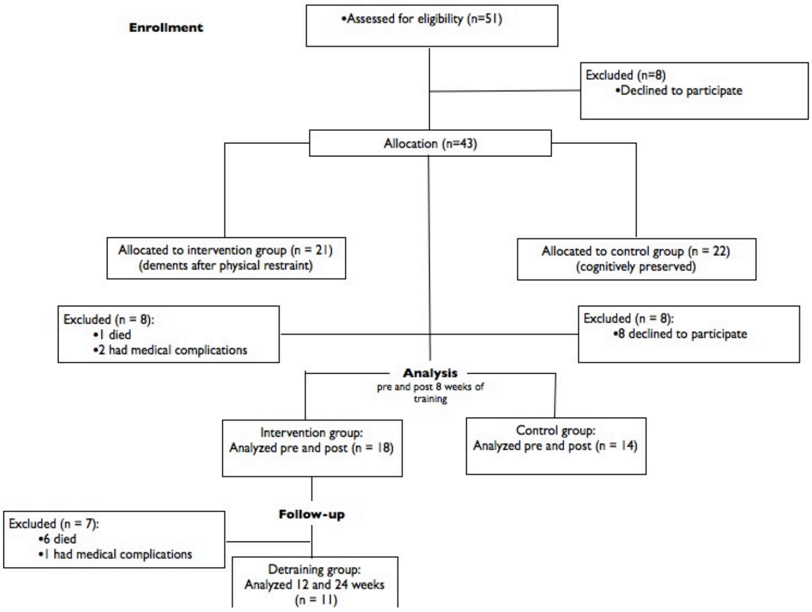

Figure 4. Flowchart for screening, recruitment, allocation, intervention and follow-up.

The total duration of the present study was 34 weeks. The first part of the trial was designed to investigate the effects of a 4-week exercise intervention that consisted of gait, balance and cognitive exercises. The second 4-week training period included a multicomponent exercise, which consisted of resistance training with loads for optimizing muscle power output. To investigate the effects of this exercise intervention on physical function in older patients with dementia after long-term physical restraint, we assessed muscle strength, functional outcomes, incidence of falls and dual-task performance. After a follow-up period of 12 and 24 weeks of training cessation, we investigated the sustainability of the physical gains. To provide the exercise intervention to all of our participants with dementia, we chose to use a period control (2 weeks) rather than a control group of elderly with dementia. Thus, we assessed the physical parameters twice before the exercise intervention to test the stability and reliability of these variables in this population. Before data collection, the individuals participated in a familiarization procedure for each test. Both before and after the intervention, each specific test was overseen by the same investigator and each test was conducted on the same equipment with identical subject/equipment positioning. Each subject performed the tests at the same time of day throughout the study**.**

3.3.3.2 Functional outcomes and incidence of falls

Gait ability was assessed using the 5-meter GVT and TUG tests. In the 5-meter habitual gait test, the subjects were asked to walk at their habitual speed on a flat 5-meter course with an initial distance of 2 meters for acceleration that was not included in the calculations of gait assessment. The TUG test consisted of measuring the time required to perform the task of standing from a chair, walking 3 meters, turning, going back to the chair, and sitting down on in the chair.

The dual-task performance was assessed using both verbal and arithmetic methods in the 5-meter habitual gait test. Gait velocity was measured during simultaneous performance a verbal or counting task (verbal GVT and counting GVT, respectively) in two separate trials. During the verbal fluency dual-task condition (verbal GVT), we measured the gait velocity as the participants named animals aloud; during the arithmetic dual-task condition (counting GVT), we measured the gait velocity while the participants counted backward aloud by ones from 100. Balance was assessed using the FICSIT-4 tests of static balance (parallel, semi-tandem, tandem and one-legged stance tests), and the subjects progressed to more difficult tests only if they had succeeded on easier tests. The chair rise test was performed to determine the maximum number of chair rises that the subjects were able to perform in 30 seconds.

Data on the incidence of falls were assessed in periods of 4 weeks: before the start of the exercise intervention (from week -4 to week 0), 4 weeks after the start of exercise intervention (week 5 to week 8) and at 12 weeks after training cessation (week 12 to week 15). Functional status was assessed using the BI, which is an international and validated tool of disability. The scores ranged from 100 (complete independence shown in daily living activities) to 0 (severe disability). The MMSE was used to measure general cognitive function.

3.3.3.3. Maximal isometric and dynamic strength

Isometric upper (right hand grip) and lower limb (right knee extensors and hip flexors) muscle strength was measured using a manual dynamometer. The maximal dynamic strength was assessed using the 1RM test with a bilateral leg press exercise. The bilateral leg press 1RM was performed using an exercise machine [Exercycle, S.L. (BH Group), Vitoria, Spain]. On the test day, the subjects warmed up with specific movements for the exercise test. Each subject's maximal load was determined with no more than five attempts, with a 4-minute recovery between attempts.

3.3.3.4 *Exercise intervention (strength and walking program)*

The total duration of the exercise program was 8 weeks. During the first 4 weeks, the participants began a short daily walk inside the nursing home, along routes normally traveled in a wheelchair; for example, going to the dining room, chapel or bathroom, or walking along the corridors of the nursing home. The participants walked using canes and walker devices, if necessary, with the assistance of a physical therapist. At all times, the participants were encouraged to increase the distance walked and to try to walk without aid. The distance was gradually increased according to the physical ability of the participants. Subjects who were in the worst physical condition (n = 8 subjects) started by walking 15.2 ± 3.2 meters per day and progressed to 33.3 ± 14.6 meters per day during the 8 weeks of intervention, whereas subjects who were in better physical condition (n = 10 subjects) started by walking approximately 60.3 ± 4.3 meters per day and progressed to 144.5 ± 37.1 meters per day. Balance and gait retraining exercises that progressed in difficulty were also implemented: semi-tandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces, and altering the base of support and weight transfer from one leg to the other. Furthermore, occupational therapy with exercises for executive and cognitive functions were also performed individually and in groups; these exercises addressed stimuli for eating and dressing, space-time orientation, reasoning, memory, language, attention and perception. In the last 4 weeks of the multicomponent exercise intervention, the participants underwent twice-weekly resistance exercises for 4 weeks with progressively increased loads (2 sets, 8-12 repetitions, 20-50% of 1RM) using a leg press machine [Exercycle, S.L. (BH Group), Vitoria, Spain]. During the progressive resistance training, the participants were instructed to perform the exercises at a high speed to optimize the power output. However, care was taken to ensure that the exercises were executed appropriately. In each session, the subjects performed a specific warm-up with one set of very light loads for the upper and lower body. All of the training sessions were carefully supervised by at least one experienced physical trainer. Attention was paid to emotional aspects, such as reassurance, respect and empathy toward the participants as described in patient-centered techniques that were developed for communication with individuals with dementia (Kitwood 1990). The simple structure of the instructions, haptic support and use of mirror techniques rather than complex oral instructions supported the progress of training and created a familiar, empathetic training atmosphere in the study group. To reduce participant dropout, music was played during all of the sessions, and adherence higher than 90% was observed in all of the subjects. Sessions were deemed completed when at least 90% of the prescribed exercises had been successfully performed.

3.3.3.5 Training cessation

After 8 weeks of the multicomponent exercise intervention, the subjects interrupted their exercise routine. They maintained their cognitive exercises in occupational therapy and also walked short distances, such as going to the bathroom and walking with assistance, but they no longer engaged in systematic physical activity.

3.3.3.6 Statistical analysis

The SPSS statistical software package was used to analyze all of the data. The normal distribution of the data was evaluated using the Shapiro-Wilk test. Statistical comparisons in the control period (from week –2 to week 0) were performed using Student’s paired t-tests. The results were reported as the mean ± SD. The training-related effects were assessed using an analysis of variance (ANOVA) with repeated measures (0, 4 and 8 weeks). When a significant F value was obtained, LSD post hoc procedures were used to evaluate pair-wise differences. Comparisons among values before and after 8 weeks of training and 12 and 24 weeks of training cessation were also performed by ANOVA with repeated measures and LSD post hoc tests in participants who were assessed during the follow-up period. $P<0.05$ was considered to be statistically significant.

3.4 RESULTS AND DISCUSSION

3.4.1 Study I

The main finding of the study I was that the frail subjects with MCI did not present different functional outcomes (i.e., gait velocity, rising from a chair, and balance performance), muscle cross-sectional area and muscle quality, as well as strength/power performance than the frail subjects with preserved cognitive function (Table 3)

Frailty syndrome is an independent predictor of a decline in cognitive function.(Samper-Ternent *et al.* 2008) Frail individuals have an increased risk of becoming cognitively impaired, and the decline in cognition over time is more severe in frail subjects as compared with non-frail subjects (Samper-Ternent *et al.* 2008; Freiberger *et al.* 2012; Buchman *et al.* 2007). In addition, impaired physical outcomes, such as altered gait velocity and muscle weakness, are associated with cognitive impairment (Samper-Ternent *et al.* 2008), and these outcomes are physical domains of frailty (Fried *et al.* 2001). In the present study, no differences were observed between the frail and frail+ MCI subjects in terms of physical function and leg muscle CSA, with both groups presenting a lower functional capacity than the non-frail subjects (Table 3). In addition to the functional outcomes, such as gait velocity, balance, and rising from a chair, we assessed muscle strength, CSA, and the incidence of falls. Although these participants were mildly cognitively impaired, the frail+ MCI subjects did not present any physical function deficits when compared with cognitively intact frail subjects. From a practical standpoint, the present results suggest that MCI does not alter physical performance in frail individuals, and exercise programs with similar physical demand may be applied in the frail elderly with and without MCI.

__Table 3__. Functional outcomes, isometric strength and muscle cross-sectional area.

	Frail + MCI (n=13)	Frail (n=20)	Non-frail (n=10)
TUG (s)	20.1 ± 7.6	19.2 ± 6.5	9.8 ± 2.1*
TUG arithmetic task (s)	22.9 ± 9.8	24.5 ± 9.3	11.4 ± 2.6*
TUG verbal task (s)	26.9 ± 10.4	26.5 ± 10.2	12.6 ± 3.6*
Cognitive Score (TUGat)	2.3 ± 0.6	1.9 ± 1.0	2.4 ± 0.5
Cognitive Score (TUGvt)	3.5 ± 1.7	7.1 ± 2.6†	5.0 ± 1.2
5-m gait test ($m{\cdot}s^{-1}$)	0.80 ± 0.16	0.69 ± 0.25	1.31 ± 0.21*
5-m gait arithmetic task ($m{\cdot}s^{-1}$)	0.66 ± 0.15	0.56 ± 0.23	1.22 ± 0.29*
5-m gait verbal task ($m{\cdot}s^{-1}$)	0.56 ± 0.11	0.51 ± 0.22	1.13 ± 0.26*
Cognitive Score (gait velocity-at)	2.5 ± 0.7	2.0 ± 0.9	2.0 ± 0.5
Cognitive Score (gait ability-vt)	4.7 ± 1.9	5.7 ± 1.8	4.4 ± 1.7
Rise from a chair	6.2 ± 3.2	6.3 ± 3.7	13.1 ± 5.7*
Incidence of falls	0.72 ± 0.46	0.95 ± 0.21	0.0 ± 0.0*
Balance score	1.54 ± 0.52	1.31 ± 0.47	2.0 ± 0.5*
Hand grip strength (kg)	15.9 ± 4.3	15.9 ± 4.3	26.8 ± 6.6*
Isometric Knee extension strength (kg)	125.5 ± 34.5	128.6 ± 44.3	216.9 ± 82.2*
Isometric Hip flexion strength (kg)	115.6 ± 27.1	90.5 ± 26.8	152.8 ± 47.2*
CSA QF_{HD} (mm^2)	6487 ± 1129	5588 ± 1581	-
CSA QF_{LD} (mm^2)	1110 ± 391	1123 ± 703	-
CSA QF_{TOT} (mm^2)	7597 ± 940	6711 ± 1693	-
CSA $Thigh_{TOT}$ (mm^2)	15220 ± 3256	13640 ± 3377	-

TUG, Time-up-and-go; at, arithmetic task; vt, verbal task; CSA, cross-sectional area; QF, quadriceps femoris; HD, high density; LD, low density; TOT, total. Comparisons between groups: *Significant different (better performance) from frail+MCI and frail groups. †Significant different (better performance) from frail + MCI group.

A possible explanation for the lack of differences in the functional tests between the two groups is that MCI and frailty are different entities on the same spectrum of disease. Several authors have included cognitive decline in the frailty phenotype because the conditions have similar pathophysiology, similar consequences (e.g., falls, hospitalization, institutionalization, and disability), and similar responses to interventions such as exercise (Makizako *et al*. 2012; Uemura *et al*. 2013; Samper-Ternent *et al*. 2008; McGough *et al*. 2011; Heyn *et al*. 2008). When tested using dual tasking, MCI gait impairments have been categorized recently (i.e., slowing gait velocity, increased gait variability) and show specific associations with executive function and the risk of falls (Maqued *et al*. 2010; Montero- Odasso *et al.* 2012). This categorization of gait impairment in the frail or frail+ MCI has not yet been studied using the dual-task paradigm. Recently, Montero-Odasso *et al*. (2012) showed that frailty is associated with low performance in several quantitative gait parameters beyond velocity, including high stride time gait variability. In addition, this variable is the most sensitive and is a stronger marker of the risk of falls than gait velocity. (Maqued *et al.* 2010; Montero- Odasso *et al.* 2012). Indeed, in the present study, the decrease in gait velocity with arithmetic tasks (dual-task cost) during the TUG test was strongly associated with the risk of falls ($r=0.78$, $P<0.01$, Table 4). From this perspective, we hypothesized that differences in stride time gait variability could help distinguish the frail and frail with MCI elderly, which was not explored in the present study.

Table 4. *Associations between Functional Tests, Incidence of Falls, and Isometric Muscle Strength in the Frail + MCI Subjects.*

	Knee extension strength	Hip flexion strength	Hand grip strength	Incidence of falls
TUG	-0.83**	-0.73**	-0.04	0.52
TUG arithmetic task	-0.83**	-0.73**	-0.30	-0.78**
5-m gait velocity	-0.76**	-0.19	-0.09	0.65**
5-m gait velocity with arithmetic task	-0.32	-0.20	-0.06	-0.56
Rise from a chair	0.41	0.76**	0.15	0.16
Incidence of falls	-0.62*	-0.39	-0.12	-
Balance	0.38	0.52	0.29	-0.56

Significant correlations: *(P <0.05) and **(P <0.01).

Although no differences between the frail and frail+ MCI groups were observed in the time spent during the TUG with a verbal task, the cognitive score during the TUG with a verbal task (i.e., a greater number of animals named) was greater in the frail group, which is likely associated with the cognitive deficits of MCI participants (Maqued *et al*. 2010; Montero- Odasso *et al*. 2012). Our results suggest that the time spent during dual tasks may not be sensitive enough to detect a worse gait ability in the frail+ MCI subjects, and the cognitive score must be considered. The absence of differences in the gait speed during the dual task tests could be related the small sample size, and this constitutes a limitation of the present study.

Sarcopenia is one of the main pathophysiological issues underlying the frailty syndrome and results in a severe decline in functional capacity (Morie *et al.* 2010; Theou *et al*. 2010); however, no studies have directly assessed the relationship between the leg CSA and functional outcomes in the frail elderly. A unique finding of the present study was the relationship observed between the quadriceps and the total thigh muscle CSA with the rising from a chair test performance, especially in the frail individuals (r=0.44-0.59, Tables 5 and 6).

Table 5*. Associations Between Functional Tests, Incidence of Falls, and Isometric Muscle Strength in the Frail Group*

	Knee extension strength	Hip flexion strength	Hand grip strength	Incidence of falls	CSA QF_{HD} (mm^2)	CSA QF_{TOT} (mm^2)	CSA $Thigh_{TOT}$ (mm^2)
TUG	-0.30	-0.43*	-0.24	0.26	-0.30	-0.39	-0.44
TUG arithmetic task	-0.21	-0.23	-0.21	0.39	-0.09	-0.07	-0.08
5-m gait velocity	-0.51*	-0.22	-0.62*	0.37	-0.30	-0.39	-0.43
5-m gait velocity with arithmetic task	-0.61**	0.06	-0.50*	0.26	-0.28	-0.41	-0.43
Rise from a chair	0.54**	0.43*	0.59*	-0.36	0.59*	0.53*	0.52*
Incidence of falls	-0.26	0.12	-0.36	-	-0.31	-0.26	-0.05
Balance	0.09	0.18	0.17	-0.32	0.23	0.13	-0.03

Hand grip strength (kg)	-	-	-	-0.36	0.65**	0.72***	0.80***
Knee extension strength (kg)	-	-	-	-0.26	0.45	0.62*	0.72***
Hip flexion strength (kg)	-	-	-	0.12	0.49*	0.49*	0.52*

Significant correlations: *(P <0.05), **(P <0.01) and ***(P<0.001).

Table 6. *Associations Between Functional Tests, Incidence of Falls, and Isometric Muscle Strength in a Whole Group of Frail and Frail + MCI Subjects*

	Knee extension strength	Hip flexion strength	Hand grip strength	Incidence of falls	CSA QF_{HD} (mm^2)	CSA QF_{TOT} (mm^2)	CSA $Thigh_{TOT}$ (mm^2)
TUG	-0.53**	-0.43**	-0.11	0.33	-0.09	-0.10	-0.22
TUG arithmetic task	-0.51**	-0.28	-0.14	0.53*	0.04	0.03	0.04
5-m gait test	-0.62**	-0.30	-0.33	0.47**	-0.27	-0.37	-0.35
5-m gait arithmetic task	-0.56**	-0.37*	-0.25	0.29	-0.22	-0.32	-0.37
Rise from a chair	0.55**	0.47**	0.36*	-0.28	0.44*	0.48*	0.51**
Incidence of falls	0.43	-0.25	-0.18	-	-0.18	-0.16	0.02
Balance	0.18	0.37*	0.19	-0.46*	0.16	0.13	-0.07
CSA QF_{HD} (mm^2)	0.35	0.43*	0.62***	-0.18	-	-	-
CSA QF_{LD} (mm^2)	0.27	0.24	0.02	0.1	-	-	-
CSA QF_{TOT} (mm^2)	0.52**	0.46*	0.68***	-0.16	-	-	-
CSA $Thigh_{TOT}$ (mm^2)	0.51**	0.43*	0.68***	-0.07	-	-	-

Significant correlations: *(P <0.05), **(P <0.01) and ***(P<0.001).

Furthermore, the muscle CSA was strongly associated with the hand grip strength in the frail subjects, and this variable has been described as a useful predictor of all-cause mortality in older populations. (Shileds *et al.*1999). Physical inactivity is a main contributor to muscle weakness, and consequently, sarcopenia generates more reduced physical activity and functional capacity, leading to disability and mortality. Nevertheless, another interesting finding of the present study was that the association between muscle CSA and functional outcomes was observed in the frail group (Table 5,) but not in the frail + MCI group (Table 6). A plausible explanation for this result is that in frail + MCI subjects, not only the neuromuscular function, but also the cognitive function influences the *functional capacity*.

Skeletal muscle power and strength in elderly people are important for the completion of activities of daily living (ADL) performance, such as rising from a chair, walking, and climbing stairs, and for reducing the incidence of falls (Reid *et al.* 2012; Izquierdo *et al.* 1999; Izquierdo *et al.* 2001, Cadore *et al.* 2012, Pereira *et al.* 2012; Bottaro *et al.* 2007). This study found important associations between muscle strength and muscle power with functional outcomes (e.g. gait ability and rising from a chair) and the incidence of falls in the frail elderly. It is important note that muscle power was assessed at a low to moderate intensity (i.e., 30 and 60% of 1RM, respectively), and both intensities were associated with functional outcomes. (Table 7)

Table 7. Associations between Muscle Power, Functional Tests, and Muscle Cross-Sectional Area in the Lower Group of Frail Subjects

	Peak power at 30% of 1RM	Peak power at 60% of 1RM
Raise from a chair	0.24	0.69*
5-m gait velocity with arithmetic task	-0.64*	-0.52
Hand grip strength (kg)	0.76***	0.56
CSA QF_{HD} (mm^2)	0.12	0.10
CSA QF_{LD} (mm^2)	0.72*	0.59*
CSA QF_{TOT} (mm^2)	0.39	0.42
CSA $Thigh_{TOT}$ (mm^2)	0.76**	0.59*

Significant correlations: *(P <0.05), **(P<0.01), and ***(P<0.001).

Based on these results, we suggest that the functional capacity in frail elderly could be improved by performing resistance training at a high speed of motion and using a low intensity of training, such as 30% of the maximal load. This result is especially important in frail subjects, who may need more frequent and longer training sessions to perform exercises at higher loads, but urgently need to improve their functional capacities to prevent adverse outcomes like falls, hospitalizations, disability, or even death.

3.4.2 Study II

The main findings of the study II were the enhancements achieved in the functional outcomes (i.e., TUG, rise from a chair, changes in BI, and balance) and reduction in the incidence of falls in institutionalised frail nonagenarians after 12 weeks of multicomponent exercise (Table 8).

Table 8. Functional outcomes, falls incidence and dual task performance.

	Exercise intervention group		Control group	
	Pre-training	Post-training	Pre-training	Post-training
Gait velocity ($m \cdot s^{-1}$)	0.76 ± 0.07	0.80 ± 0.08	0.68 ± 0.06	0.60 ± 0.07*
TUG (s)	19.9 ± 8.0	18.8 ± 7.9*†	18.4 ± 5.1	21.8 ± 6.3
Raise from a chair	6.2 ± 4.1	9.8 ± 6.0**†	6.3 ± 3.4	5.4 ± 3.9
Balance	0.44 ± 0.5	0.66 ± 0.5	0.36 ± 0.5	0.3 ± 0.5
Gait velocity arithmetic task ($m \cdot s^{-1}$)	0.60 ± 0.08	0.61 ± 0.07	0.56 ± 0.05	0.49 ± 0.06*
Cognitive Score (arithmetic)	2.1 ± 0.9	2.6 ± 0.5	2.2 ± 0.8	2.1 ± 0.9
Gait velocity verbal task ($m \cdot s^{-1}$)	0.53 ± 0.06	0.59 ± 0.06	0.50 ± 0.05	0.46 ± 0.06*
Cognitive Score (verbal)	5.6 ± 1.7	5.6 ± 1.0	5.5 ± 1.8	5.6 ± 1.7
Falls incidence	0.77 ± 0.44	0.0 ± 0.0***†+	0.93 ± 0.3	0.8 ± 0.4
TUG arithmetic task (s)	23.8 ± 11.4	20.7 ± 7.0†	22.7 ± 6.2	23.5 ± 7.4
Cognitive Score (TUG arithmetic)	2.3 ± 0.9	2.4 ± 1.0	1.8 ± 1.0	1.9 ± 0.8
TUG verbal task (s)	25.7 ± 11.5	22.4 ± 8.5*†	22.8 ± 5.0	26.1 ± 8.2
Cognitive Score (TUG verbal)	6.2 ± 3.0	6.5 ± 2.7	6.7 ± 2.7	6.6 ± 1.0
BARTHEL INDEX deterioration	-	0.09 ± 0.30 +	-	0.60 ± 0.52

TUG, time-up-and-go test. Significant difference from pre-training values: *(P<0.05), **(P<0.01), ***(P<0.001); Significant time vs. group interaction: †(P<0.05). Significant difference between groups after training +(P<0.001).

Before the exercise intervention, there were no differences between groups in any of the functional outcomes (i.e., gait velocity, TUG, rise from a chair test, balance, and BI) or fall incidence. After training, there was a significant time vs. group interaction in the 5-m habitual gait velocity ($P<0.05$), TUG ($P<0.01$), rise from a chair ($P<0.01$), balance ($P<0.05$), and incidence of falls ($P<0.001$).

After training, the incidence of falls was significantly lower in the intervention group compared with the control group ($P<0.001$). In addition, the intervention group showed significantly lower deterioration in the BI compared with the control group after training. Furthermore, the intervention group tended to perform better on the rise from a chair test than the control group after the intervention ($P=0.069$). (Figure 5)

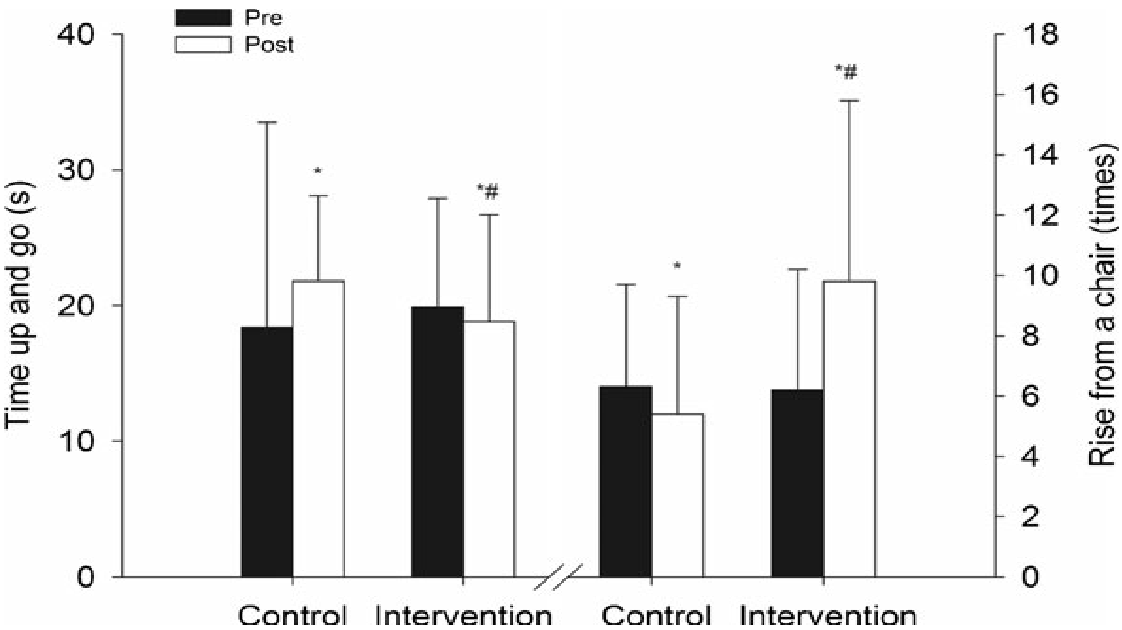

Fig. 5 Time-up-and-go (s) and rise from a chair (times) tests (mean±SD). Significant difference from pre-training values: *P<0.05. Significant time vs. group interaction: # P<0.05.

In addition, there was an improvement in the TUG with verbal task performance in the intervention group, whereas decreases were observed in dual-task performance in the control group (Table 8).

Frail nonagerians participants of the present study increased their maximal dynamic strength (1RM) and power output values. (Table 9) Before the exercise intervention, there were no differences between groups in any strength variables. After training, there was a significant time vs. group interaction in the isometric hand grip ($P<0.01$), hip flexion ($P<0.05$), and knee extension ($P<0.01$) strength. The intervention group showed significant increases in isometric hip flexion (27.2±9.5 %, $P<0.01$) and knee extension strength (23.6±10.3 %,$P<0.05$), whereas no significant changes were observed in isometric hand grip. In contrast, significant decreases were observed in the isometric hand grip and knee extension strength in the control group ($P<0.01$), whereas no change was observed in the isometric hip flexion strength in this group.

Table 9. Strength, power and velocity outcomes before and after exercise intervention (Mean ± SD):

	Exercise intervention group		Control group	
	Pre-training	Post-training	Pre-training	Post-training
Hand grip (N)	165 ± 63	183 ± 52†+	157 ± 64	130 ± 58*
Hip flexion strength (N)	1057 ± 262	1284 ± 203**†+	865 ± 268	834 ± 382
Knee extension strength (N)	1451 ± 441	1745 ± 460*†+	1206 ± 336	1042 ± 353*
Upper-body 1RM (kg)	16.4 ± 9.6	26.7 ± 12***	-	-
Lower-body 1RM (kg)	77.1 ± 26.3	188.6 ± 48.1***	-	-
Maximal power at 30% 1RM (W)	83.8 ± 63.4	165.2 ± 107.4**	-	-
Maximal power at 60% 1RM (W)	165.9 ± 62.6	360.1 ± 184.2**	-	-

There were significant increases in the maximal dynamic strength (1RM) and power values assessed in the exercise intervention group. Significant changes over time were observed in the lower body 1RM (144 %, $P<0.001$), maximal power at 30 % of 1RM (96 %, $P<0.01$), maximal power at 60 % of 1RM (116 %, $P<0.01$), and upper body 1RM (68 %, $P<0.001$). (Table 9)

A unique finding was that the institutionalized oldest old participants of the present study were able to improve their quadriceps femoris and knee flexor muscle CSA, and this CSA increase occurred only in the high-density muscle tissue (i.e., low fat infiltration). There were significant time vs. group interactions in the CSA of the high-density quadriceps femoris muscles (P<0.05), total quadriceps femoris muscles (P<0.05), high-density knee flexors muscles (P<0.05), and total knee flexors muscles (P<0.01). (Table 10)

Table 10. Cross-sectional area of the thigh muscles (mm^2) (Mean ± SD).

	Exercise intervention group		Control group	
	Pre-training	Post-training	Pre-training	Post-training
CSA QF HD (mm^2)	5350 ± 1319	5610 ± 1249*†	6194 ± 1095	5997 ± 1006
CSA QF LD (mm^2)	1387 ± 723	1394 ± 788	685 ± 146	723 ± 128
CSA QF TOT (mm^2)	6738 ± 1609	7004 ± 1700*†	6879 ± 1107	6720 ± 1071
CSA Thigh TOT (mm^2)	13856 ± 3292	14321 ± 3385	13981 ± 2464	13399 ± 2462
CSA KF HD (mm^2)	1383 ± 540	1486 ± 474†	1398 ± 529	1244 ± 470
CSA KF LD (mm^2)	872 ± 318	949 ± 375	1087 ± 240	1131 ± 168
CSA KF TOT (mm^2)	2256 ± 725	2436 ± 685**†	2485 ± 679	2375 ± 561
CSA ADD TOT (mm^2)	13856 ± 3292	14321 ± 3385	13981 ± 2464	13399 ± 2462
CSA Thigh TOT (mm^2)	3910 ± 1793	3914 ± 1808	3258 ± 1029	3040 ± 1273

CSA, muscle cross-sectional area; QF, quadriceps femoris; HD, high-density tissue (low fat infiltration); LD, low density tissue (high fat infiltration); TOT, total; KF, knee flexors; ADD, hip adductors. Significant difference from pre-training values: *(P<0.05), ** (P<0.01); and significant time vs. group interaction: †(P<0.05).

Moreover, there was a trend towards a significant time vs. group interaction in the CSA of the total thigh muscle (P<0.07). There were significant increases in the CSA of the high-density quadriceps femoris (P<0.05), total quadriceps femoris (P<0.05), and total knee flexormuscles (P<0.01) only in the intervention group, whereas no changes were observed in the control group (Table 10 and Fig. 6).

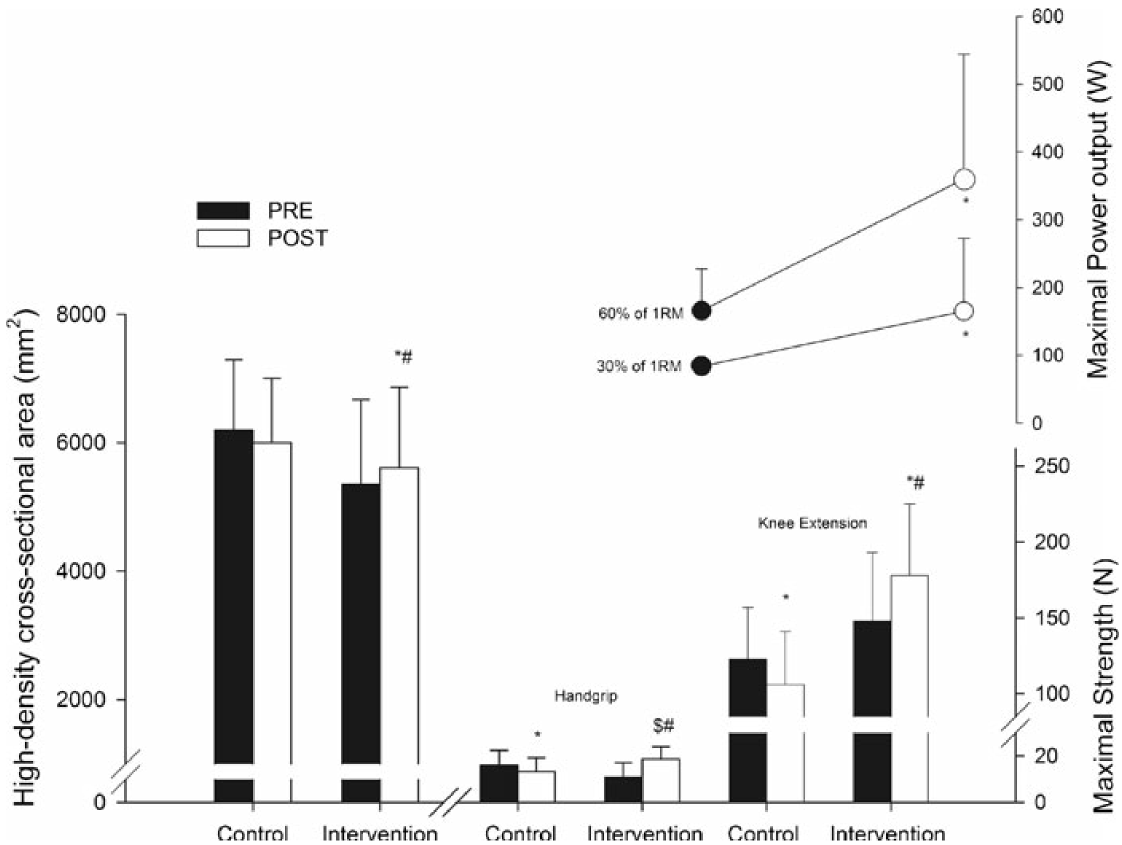

Figure 6. Quadriceps femoris high-density cross-sectional area (mm^2), maximal isometric hand grip and knee extension strength (N), and maximal power output (W) at 30% and 60% of maximal dynamic strength (1RM) (Mean ± SD). Significant difference from pre-training values: *(P<0.05). Significant time vs. group interaction: #(P<0.05). Significant difference between groups after intervention: $(P<0.01).

In addition, there was a trend towards a significant increase in the CSA of the high-density knee flexors muscles (i.e area with low intramuscular fat tissue and high muscle quality) only in the intervention group (P<0.06). In contrast, after training, no changes were observed in the low density quadriceps femoris and knee flexor muscles, as well as in the total hip adductors muscles in the intervention and control groups (Table 10).

These results are interesting because in institutionalized frail nonagenarians, a multicomponent exercise program that included muscle power training induced a positive stimulus to promote muscle hypertrophy, decrease the fat muscle infiltration, enhance leg muscle power and functional capacity, and decrease the incidence of falls.

Few studies have addressed the physiological and functional adaptations to exercise intervention in institutionalized frail nonagenarians. Fiatarone *et al.* (1994)

investigated physically frail elderly subjects (72 to 98 years) and showed that the resistance training improved the subjects' functional abilities and strength. In another study by Serra-Rexach *et al.* (2011), oldest old subjects (90–97 years of age) underwent resistance and endurance training and increased their leg press strength, but no changes were observed in their gait ability. In the present study, the nonagenarians performed a multicomponent exercise program composed of high-speed resistance training and balance and gait exercises. This exercise intervention induced improvements in not only strength but also several parameters of functional capacity in the oldest old.

The positive effects of exercise on functional capacity may be more often observed when more than one physical conditioning component (i.e., strength, endurance, or balance) is included in the exercise intervention compared with only one type of exercise (Cadore *et al.* 2013). Our results are in agreement with a previous study that investigated the effects of multicomponent exercise interventions in the frail elderly. Lord *et al.* (2003) found that 12 weeks of an intervention that included gait, balance, and weight-bearing exercises resulted in 22 % fewer falls in frail elderly individuals compared with control subjects. In addition, Binder *et al.* (2002) showed significant improvements in balance and physical performance scores in the physically frail elderly after 36 weeks of multicomponent exercise intervention. In another study, recently, Clemson *et al.* (2012) demonstrated a reduction in the incidence of falls (31 %) and greater strength and balance performance after 12 months of multicomponent exercise intervention. Multicomponent exercise intervention has also induced positive effects in gait velocity, and 16 weeks of training significantly improved this functional parameter (Freiberger *et al.* 2012). Our results showed that multicomponent exercise intervention may also be tolerated by frail nonagenarians and enhance their capacity to perform daily activities and reduce the incidence of falls. A possible explanation to the marked increases in the functional capacity in our subjects could be related to the improvements observed in the muscle CSA and power output, because a cross sectional study has showed that the functional outcomes are strongly associated with muscle CSA and power output in frail nonagenarians (Casas-Herrero *et al.* 2013).

The frail oldest old in the present study reduced their time spent on performing the TUG test with a verbal task (i.e., naming animals), whereas the control group showed reduced gait velocity during the 5-m habitual gait with verbal and arithmetic tasks (Table 8). Therefore, we suggest that positive multicomponent training-induced changes in the dual-task cost in the frail oldest old may be related to achievements in executive function. In agreement with this hypothesis, exercise training improves not only the physical but also the cognitive performance in elderly populations (Heyn *et al.* 2008). The effects of exercise training on dual-task gait performance in the frail oldest old have been poorly investigated. Thus, the present study extends the knowledge regarding dual-task exercise adaptations to exercise intervention. There may be a "dual-task cost" in frail individuals when they change from a single to dual task (Montero-Odasso *et al.* 2012). After the exercise intervention, the frail nonagenarians in the present study presented the same cognitive score during the TUG with a verbal task but completed the test in a significantly lower time, which suggests that they reduced the dual-task cost. This result is important because we recently observed a strong correlation between TUG with verbal task and the incidence of falls in nonagenarians (Casas-Herrero *et al.* 2013). Moreover, although the exercise intervention was unable to improve their performance during the dual-task 5-m gait velocity test in the intervention group, the intervention seems to have preserved the dual-task cost in this group, whereas the control group showed reduced gait velocity in these tests.

Despite the strength adaptations previously observed in the oldest old (Fiatarone *et al.* 1994; Serra- Rexach *et al*. 2011), to the best of our knowledge, this is the first study to investigate the performance of high speed resistance training in frail nonagenarians subjects, and this study demonstrated that these subjects maintained their capacity to improve muscle power output, which occurred at light to moderate intensities (i.e., 30 and 60 % of 1RM). These results are interesting because first, skeletal muscle power decreases earlier and faster than muscle strength with advancing age (Izquierdo *et al.* 1999), and second, as mentioned above, muscle power seems to be more closely associated with performance on functional tests than muscle strength per se in the elderly populations (Cadore and Izquierdo 2013; Reid and Fielding 2012; Casas- Herrero *et al.* 2013). Along with the increased muscle CSA observed in the present study, neural adaptations such as the increase in the maximal motor unit recruitment and maximal motor unit firing rate may help to explain the strength and power output increases observed in the present study (Cadore and Izquierdo 2013).

3.4.3 Study III

The main finding of the study III was that after several months of physical restraint, a multicomponent exercise intervention program composed of walking, muscle power training, cognitive and balance exercises provides an optimal stimulus for improving muscle strength, balance and gait ability and for reducing the incidence of falls in frail patients with dementia. Additionally, the changes in muscle strength and gait ability occurred primarily after the second half of the intervention (last 4 weeks), during which resistance training with a special emphasis in power output development was included.

During the control period, there were no changes in the intervention group in any of the physical outcomes assessed. After the first period of training (i.e., 4 weeks of gait and cognitive exercises), there were no changes in the 5-meter gait velocity test, TUG, dual-task performance or rising from a chair, whereas a significant enhancement of balance was observed (Table 11). However, after the second part of the training period (i.e., 4 weeks of multicomponent exercise including resistance training with loads that optimize muscle power output), the intervention group required significantly less time for the TUG test ($P<0.05$) and tended to have a higher gait velocity in the 5-meter test, although the difference did not reach significance ($P=0.07$) (Figure 7). A significant reduction was also observed in the incidence of falls ($P<0.01$). No changes were observed in the intervention group in the BI score, MMSE, dual-task performance and rising from a chair, and no additional change was observed in balance.

Table 11. Functional and strength outcomes pre and post the intervention and follow-up period (mean ± SD):

	Exercise intervention group (n=18) and follow-up group (n=11)				
	Intervention period			Follow-up period	
	Pre	Post 4 weeks of intervention	Post 8 weeks of intervention	12 weeks of detraining	24 weeks of detraining
Gait velocity ($m·s^{-1}$)	0.36 ± 0.18	0.32 ± 0.21	0.42 ± 0.21	0.30 ± 0.20*†	0.25 ± 0.17*†$
TUG (s)	43.4 ± 16.3	49.4 ± 55.7	31.2 ± 10.9*	55.4 ± 32.6*†	62.7 ± 38.5†

Raise from a chair	2.3 ± 3.5	1.4 ± 3.4	2.7 ± 4.0	2.2 ± 2.8	1.8 ± 2.2
Balance	0.30 ± 0.5	0.82 ± 0.8*	0.80 ± 0.7*	0.90 ± 0.8	0.70 ± 0.8
Gait velocity arithmetic task (m·s^{-1})	0.27 ± 0.21	0.28 ± 0.24	0.29 ± 0.17	0.18 ± 0.14*†	0.17 ± 0.12*†
Gait velocity verbal task (m·s^{-1})	0.27 ± 0.17	0.24 ± 0.19	0.27 ± 0.17	0.21 ± 0.16*†	0.19 ± 0.14*†
Incidence of falls	1.1 ± 1.4	-	0.16 ± 0.5*	0.30 ± 0.60†	-
Barthex index	35.0 ± 18.1	29.6 ± 18.1	30.3 ± 17.7	23.3 ± 16.3*†	18.3 ± 14.1*†
MMSE	15.1 ± 6.3	15.6 ± 6.7	15.9 ± 7.1	12.6 ± 4.2†	10.6 ± 3.1*†$
Hand grip (kg)	11.9 ± 4.6	12.9 ± 5.8	13.8 ± 5.3*	10.7 ± 4.8*†	9.4 ± 4.2*†$
Knee extension strength (kg)	14.3 ± 5.9	15.7 ± 5.5	17.3 ± 4.5*	11.1 ± 3.7*†	8.5 ± 2.6*†$
Hip flexion strength (kg)	13.9 ± 4.7	12.5 ± 5.1	16.7 ± 4.5*	11.0 ± 2.9*†	9.0 ± 2.0*†$
Lower-body 1RM (kg)	33.5 ± 13.4	31.4 ± 15.6	43.9 ± 16.4*	37.0 ± 15.7	32.5 ± 12.0†

TUG, time-up-and-go test; 1RM, one maximum repetition. MMES, Mini-mental state examination. Significant difference from pre-training values *(P<0.05); Significant difference from post 8 weeks of training †(P<0.05); Significant difference from post 12 weeks of detraining $(P<0.05).

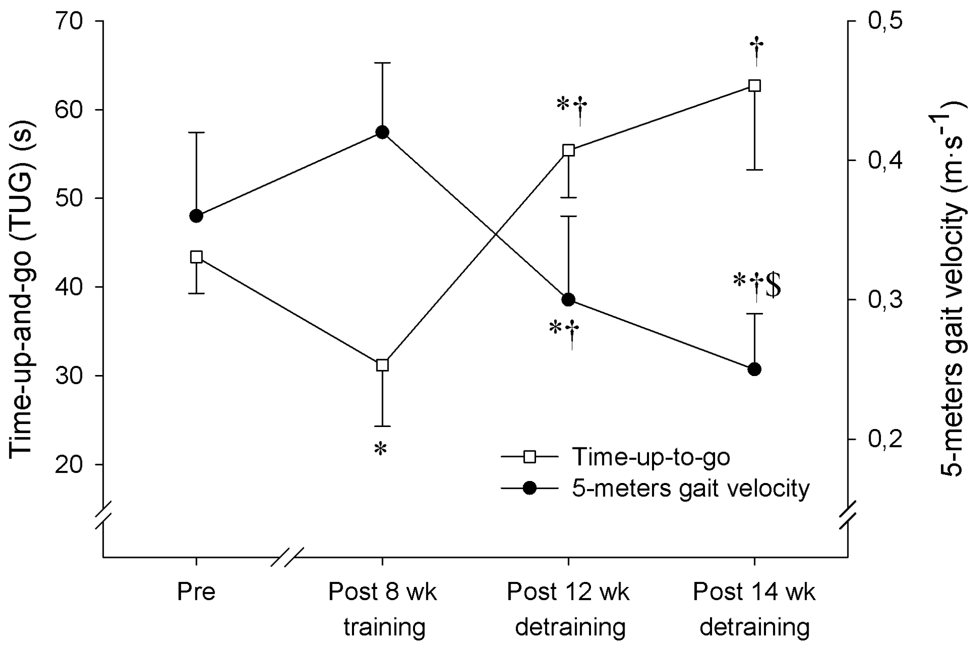

Fig. 7 Time-up-and-go (TUG) (s) and gait velocity tests (m·s-1) (Mean ± SD) pre, post 8 weeks of training, post 12 weeks of detraining, and 24 weeks of detraining. Significant differences from pre training values *(P<0.05); and, significant difference from 8 weeks of training †(P<0.05).

After the first period of training (i.e., 4 weeks of gait and cognitive exercises), there were no changes in the isometric hand grip, knee extension and hip flexion strength, or in the maximal dynamic strength (1RM). After the second part of the training period, the intervention group showed significant increases in isometric hand grip, hip flexion and knee extension strength (P<0.01). Significant changes were also observed in the lower body 1RM in the intervention group. (Figure 8)

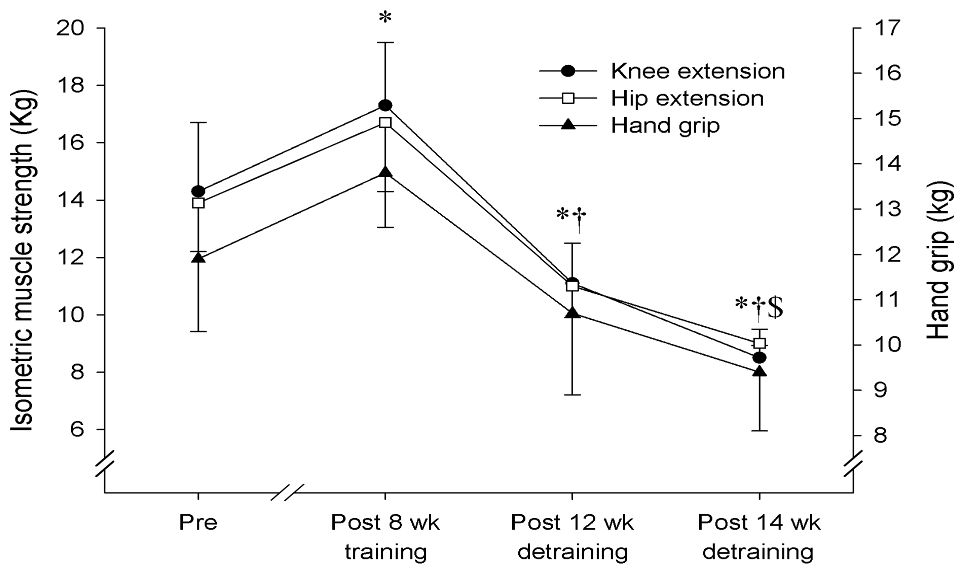

Figure 8. Knee extension, hand grip and hip flexion isometric strength (Kgf) (Mean ± SD) pre, post 8 weeks of training, post 12 weeks of detraining, and 24 weeks of detraining. Significant differences from pre training values *(P<0.05); significant difference from 8 weeks of training †(P<0.05); and, significant difference from 12 weeks of detraining $(P<0.05).

After 12 and 24 weeks of training cessation, significant decreases were observed in nearly all of the variables assessed (Table 11). Regarding the strength variables, the isometric hand grip, knee extension and hip flexion strength were lower after 12 and 24 weeks of detraining compared with before training and after 8 weeks of intervention (P<0.05), with the values after 24 weeks being lower than those after 12 weeks of detraining (P<0.05) (Figure 8). The lower-body 1RM strength after 24 weeks of detraining were lower than that after 8 weeks of exercise intervention (P<0.05).) Regarding functional outcomes, the gait speed with single and dual tasks (both verbal and arithmetic tasks) was lower after 12 and 24 weeks of detraining compared with before training and after 8 weeks of intervention (P<0.05). TUG performance was significantly decreased after 12 and 24 weeks of detraining, with more time spent during the test after 12 and 24 weeks of detraining compared with before training and after 8 weeks of intervention. Additionally, the TUG tended to require more time after 24 weeks of detraining than after 12 weeks of detraining, although the difference did not reach significance (P=0.06) (Figure 7). The incidence of falls significantly decreased after 12 weeks of detraining (P<0.05). Moreover, significantly lower values were observed in the BI score after 12 and 24 weeks of training compared with values before and after training (P<0.05). Furthermore, significant reductions in the MMSE score were observed after 12 and 24 weeks of training compared with the pre and post training scores (P<0.05). No changes were observed in chair rise performance or balance during the detraining period (Table 11).

These results suggest that even after long-term physical restraint, frail elderly patients with dementia and disability maintain their capability to improve strength and functional capacity and that a multicomponent exercise intervention that includes muscle power training seems to be effective in providing these changes.

Hauer *et al.* (2012) found that 3 months of progressive resistance and functional training resulted in significant increases in maximal strength and functional performance in elderly patients with dementia. Liu-Ambrose *et al.* (2010) showed significant improvement of executive functions and maximal peak power, but not gait speed, after 12 months of strength training in patients with dementia. However, in these studies, the patients with dementia were capable of walking 10 m without a walking aid (Hauer *et al.*. 2012) or were living independently in their own home (Liu-Ambrose *et al.* 2010), which suggests that the patients in these studies had a better functional status than the patients in the present study. Thus, although previous studies have shown positive effects of strength and endurance training in elderly patients with cognitive impairment and dementia (Heyn *et al.* 2004, 2008) this report is the first to investigate frail patients after several months of physical restraint. Physical restraints, which are often used in elderly individuals who require long-term nursing care (Zwijsen *et al.* 2011), limit the freedom of movement (Hantikainen 1998; Hamers and Huizing 2005), which results in severe adverse outcomes, such as exacerbated sarcopenia, decreased muscle quality, rapid strength loss, impaired ability to stand and walk and overall decreased functional status and quality of life (Suetta *et al.* 2007;

Gulpers *et al.* 2010; Zwijsen *et al.* 2011; Berzlanovich *et al.* 2012). Thus, effective strategies to increase physical activity and independence with a low risk of falls are required. In the present study, only 8 weeks of a multicomponent exercise program composed of resistance training, walking and cognitive exercises improved strength, balance and TUG performance, and reduced the incidence of falls. The TUG test is a simple and classic test for evaluating the risk of falling in elderly patients. In frail elderly patients, a cut-off point of 12 seconds has been suggested, with no clear references for dementia patients. In our study, the participants in the intervention group showed a significant decrease in the time required to perform the TUG, which suggests a decreased risk of falls in this sample of very old frail patients with dementia. This finding is remarkable, considering that this population has a high incidence of falling and a significant risk for falling (Casas-Herrero *et al.* 2011; Robertson *et al.* 2013).

The participants' physical improvement occurred primarily after the inclusion of twice-weekly resistance training with a special emphasis on power output development. Resistance training performed with high-speed motion in the concentric phase has been shown to be effective in improving the functional capacity of healthy younger elderly patients (Bottaro *et al.* 2007; Correa *et al.* 2012; Pereira *et al* 2012b), which suggests that this type of training may improve the functional capacity in subjects with a poor physical condition, as demonstrated in the frail elderly patients with dementia in the present study. The absence of changes in other fall risk predictors, such as the dual-task performance, or in functional measurements such as the Barthel Index and rising from a chair suggests that a longer exercise intervention or greater volume of resistance, walking and balance exercises may be necessary to stimulate additional changes.

In the present study, the walking program consisted of a daily walk on routes previously traveled in a wheelchair, such as going to the bathroom and to the dining room, and in the corridors of the nursing home. The subjects increased their amount of walking; therefore, this walking program was an important parameter related to functional capacity. Additionally, most of the patients changed from using a wheelchair to using canes and walker devices, which also represented a relevant subjective parameter related to their level of independence, functional status and total amount of physical activity.

The purpose of the present study was to investigate a follow-up period with no systematic physical activity after the exercise intervention because it would be interesting to determine the capacity of this population to retain strength and functional gains. Another important finding of the present study was that the intervention group showed severely decreased physical and cognitive outcomes after the cessation of training. At several weeks after cessation of high-speed resistance training, healthy elderly patients retained a portion of their functional capacity gains (Pereira *et al.* 2012a), which was not observed in the patients with dementia and disability in the present study. In addition to their clinical condition, the absence of residual training effects most likely resulted from their physical status as a consequence of the long-term physical restraint used in their nursing care. This poor clinical condition became more evident after 3 and 6 months of detraining, during which the frail patients presented values lower than those in the pretraining period. These results are in agreement with the observed decrease in physical outcome performance after interruption of the exercise intervention in the frail elderly (Hauer *et al.* 2012; Zech *et al.* 2012). After analyzing the follow-up data, we suggest that, in addition to the improvements observed in the strength outcomes, balance, incidence of falls and TUG performance, the exercise intervention was also responsible for maintaining the overall physical function in this population because during the detraining period, the physical performance deteriorated to a lower level than the pretraining value. These results reinforce the need for this population to be involved in an exercise intervention composed of high-speed resistance training together with gait and balance retraining (i.e., a multicomponent exercise program).

CONCLUSIONS

1. Multicomponent exercise programs are efficient strategies to prevent disability and other frailty domains such falls, cognitive decline and depression in frail aged patients. However, it is necessary to explore optimal resistance training components and develop specific clinical guides of physical activity for this target population **(Review article).**

2. Frail subjects with MCI did not present different physical outcomes than the frail subjects with preserved cognitive function. Functional outcomes, such as gait velocity, rising from a chair, balance performance, and the incidence of falls, were associated with muscle mass, strength, and power performance in the frail elderly. Based on the present results, we suggest that in addition to strength stimulation, power and velocity of motion with light loads (30% of 1RM) must be stimulated to improve functional capacity in the frail elderly. **(Study I)**

3. A multicomponent exercise intervention used in frail nonagerians institutionalized participants resulted in improvements in strength and power performance, muscle hypertrophy, intramuscular fat infiltration, and functional outcomes (i.e., TUG, rise from a chair, balance, and dual task performance) and reduced the incidence of falls in institutionalized frail nonagenarians. **(Study II)**

4. From a practical standpoint, routine multicomponent exercise intervention composed of resistance training, balance training, and gait exercises should be included for nonagenarians because it seems to be the most effective intervention for improving the overall physical outcomes of frail nonagenarians and preventing disability and other adverse outcomes. **(Study II)**

5. A systematic multicomponent exercise intervention in frail aged institutionalized participants with dementia resulted in improvements in muscle strength, balance and gait ability and decreased the incidence of falls in frail elderly patients with dementia after long-term physical restraint. We should emphasize that the physical enhancements observed in the participants occurred primarily after the inclusion of twice-weekly resistance training with a special emphasis on power output development. **(Study III)**

6. Additionally, the absence of changes when patients rose from a chair or in dual-task performance or the Barthel Index scores suggests that a longer intervention or perhaps a higher volume of resistance exercises may be necessary to stimulate more changes. After 12 and 24 weeks of exercise interruption, frail patients with dementia presented worse values than in the pretraining period, which reinforces the need for this population to be involved in a multicomponent exercise intervention that consists of resistance training in addition to gait and balance retraining. **(Study III)**

7. **LIST OF SCIENTIFIC ARTICLES**

Study I: Casas-Herrero A, Cadore E, Zambon –Ferraresi *et al*. Functional capacity, muscle fat infiltration, power output and cognitive impairment in institutionalized frail oldest old. Rejuvenation Res 2013. Jul 3

Study II: Cadore E, Casas Herrero A, Zambon-Ferraresi F *et al.* . Multicomponent exercises including muscle power training enhance muscle mass, power output and functional outcomes in institucionalized frail nonagerians. Age (Dordr). 2013 Sep 13.

StudyIII: Eduardo L. Cadore, Ana B. Bays Moneo, Marta Martinez Mensat, Andrea Rozas Muñoz, Alvaro Casas-Herrero Leocadio Rodriguez-Mañas, Mikel Izquierdo. Positive effects of resistance training in frail elderly patients with dementia after long-term physical restraint. Submitted